



USING SPECTRAL METHODS ON HIV INFECTION WITH TAT AND SSU72 ACTIVATION

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Abstract

HIV dynamics within the host are complex especially when a reservoir of latently infected $CD4^+$ T cells are present. The failure of the immune system and antiviral therapy to suppress the virus has been suggested to be enhanced by the latently infected $CD4^+$ T cells which are responsible for persistence of HIV within the host. Cells remaining in latent state have been shown to lack sufficient levels of Tat and associated activation-dependent host factor that are necessary for processive transcription of the virus. Tat is a protein that is capable of activating the latently infected $CD4^+$ T cells. Recently, as a protein, Ssu72 was found to be responsible for activation and replication of the virus. Ssu72 enhances the effects of Tat activation in a mutualistic interactive manner. The interaction of Tat and Ssu72 thus, enhances the activation of the latently infected $CD4^+$ T cells which may in turn expose the virus for possible attack by the immune system reaction. In the current study, we modify a constant virus HIV model to incorporate the effects of Tat and Ssu72 on latently infected $CD4^+$ T cells. We analyze the models using both analytic and numerical techniques. Important threshold was derived and model analysis carried out. The incorporation of Tat and Ssu72 proteins on the HIV-1 model with a constant virus shows that, with time the uninfected and infectious classes decrease to zero for a threshold value of 30-40 copies of each protein.

Declaration

I, S'yanda Nkanyiso Mungwe, declare that

1. The research reported in this thesis, except where otherwise indicated, is my original research.
2. This thesis has not been submitted for any degree or examination at any other university.
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Student's Signature Date: /04/2016.

Supervisor's Signature Date: /04/2016.

Co-Supervisor's Signature Date: /04/2016.

Dedication

I wish to dedicate this study to Rev M.V. Mabaso (Grandfather), Mrs B. KanaMabaso Zulu (Mother), Mr S.E. Mabaso (Uncle), Mr N.L. Mungwe (Brother), and to the rest of the family and friends. More especially, I'll like to dedicate this study to my late Grandmother Mrs T.B. KamaZikalala Mabaso.

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Contents

Abstract	i
Declaration	i
Dedication	ii
Acknowledgements	iii
1 Introduction	1
1.1 Background	1
1.2 Research question	5
1.3 Problem statement	5
1.4 Aim	6
1.5 Objectives	6
1.6 Significance of the study	6
1.7 Scope of the study	7
2 Literature Review	8
2.1 Introduction of HIV-1 infection dynamics	8
2.2 HIV-1 Tat	11

2.3	Ssu72 Protein	12
2.4	Preliminaries	14
2.4.1	Existence of solutions [29]	14
2.4.2	Equilibrium state [29]	14
2.4.3	Stability [29]	15
2.4.4	Center manifold theorem [31]	15
2.4.5	Descartes rule of signs [30]	17
3	HIV-1 model with a constant virus production	18
3.1	Introduction	18
3.2	Model formulation	18
3.3	Feasible region of the model	21
3.3.1	Disease free equilibrium point	25
3.3.2	Basic reproduction number	25
3.4	Endemic equilibrium point	28
3.5	Stability analysis of equilibrium points	30
3.5.1	Local stability of DFE	31
3.5.2	Global stability of the DFE	33
3.5.3	Stability analysis of endemic equilibrium	35
3.6	Summary	38
4	Analysing HIV-1 model incorporating Tat and Ssu72 proteins	40
4.1	Introduction	40
4.2	Model formulation	41
4.3	Analysis of Tat and Ssu72 model	44

4.3.1	Equilibrium points for Tat and Ssu72 dynamics model	44
4.3.2	Stability analysis of equilibria of Tat and Ssu72 dynamics	44
4.4	summary	46
5	Multistage spectral relaxation method algorithm	48
5.1	Introduction	48
5.2	Multistage spectral relaxation method	50
5.3	Algorithm	51
5.3.1	Application of the MSRM on the model incorporating Tat and Ssu72	54
5.4	Summary	57
6	Numerical simulations	59
6.1	Introduction	59
6.2	Simulation of results: $\pi_1 = 1$ and $\pi_1 = 10$	62
6.3	Discussion of results: $\pi_1 = 1$ and $\pi_1 = 10$	62
6.4	Summary	71
7	Discussion and conclusion	73
7.1	Conclusion	75
7.2	Further work	76

List of Figures

3.1	Model showing the interaction of the compartments	21
6.1	Results of the model without Tat and Ssu72, when $\pi_1 = 1$. . .	63
6.2	Results of the model without Ssu72, when $\pi_1 = 1$	64
6.3	Results of the model without Tat, when $\pi_1 = 1$	65
6.4	Results of the model with Tat and Ssu72, when $\pi_1 = 1$	66
6.5	Results of the model without Tat and Ssu72, when $\pi_1 = 10$. . .	67
6.6	Results of the model without Ssu72, when $\pi_1 = 10$	68
6.7	Results of the model without Tat, when $\pi_1 = 10$	69
6.8	Results of the model with Tat and Ssu72, when $\pi_1 = 10$	70

List of Tables

6.1	Estimated values of parameters	61
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Chapter 1

Introduction

1.1 Background

In 2013, South Africa was estimated to be the leading country in cases of people living with HIV-1. About 6.3 [6-6.5] million cases of people living with HIV-1 [1] and about 200,000 [170,000 - 220,000] death due to AIDS [1] were estimated in South Africa. In 2014, 36.9 million [34.3 million - 41.4 million] people globally were living with HIV. According to the 2014 global statistics by UNAIDS, the new HIV infection have fallen by 35% since 2000. However, there have been 2 million [1.9 million - 2.2 million] new cases reported of people infected with HIV [2]. Despite the existence of intervention strategies, there has been new cases of people living with HIV-1 reported [21].

HIV-1 is a virus that attack immune system making it weak to fight off any infections [19]. HIV-1 is described by a progressive loss of $CD4^+$ T cells, as well as excessive immune activation and poor control of the virus by T cells in

most individuals [14]. This has led to many studies conducted to understand the dynamics of the virus. However, there exist no vaccine for HIV up to date [17]. Hence, if an individual has acquired the virus, the subject remains with it not cured but only treated. The antiretroviral treatment is one of the intervention strategies that has to be initiated to the infected subject [21].

Due to a statistical increase in new cases of people living with HIV-1, the roll-out or distribution of ARVs had to increase. But the distribution of the drug is costly [22], which calls for new intervention treatment strategies. In most Sub-Saharan countries an individual initiates ARV when the subject's CD4 count is 200 cell/ μ l or less [17, 22]. Most studies have disputed this threshold. An estimate of 42% of people living with HIV in developing countries have access to ARVs [22]. The high active antiretroviral treatment (HAART), helps the immune system to effectively suppresses the virus replication [4]. This leads to the increase of the number of CD4⁺T-lymphocyte, which directly leads to a degree of immune reconstitution that is sufficient to reverse clinically apparent immunodeficiency [4].

The murine and animal models have shed light on the importance of CD4⁺ T helper cells in the control of chronic viral infection [11]. These results revealed the importance of CD4⁺ T cells and CD8⁺ T cells interplay in the maintenance of potent and effective immune response that is able to control chronic viral infections [4, 11]. According to [22], the CD4⁺ T helper cell responses are essential for eliminating virus during the acute phase of disease and must be permanently maintained to achieve long-time viral control

[4, 11, 19]. The depletion of $CD8^+$ T cells in chronic phase lead to increase in viral load [11], which progressively leads to viral replication that in turn further impairs the functionality of immune system.

According to the report on $CD4^+$ T cell count in HIV patients [19], HIV primary target immune cells called $CD4^+$ T cells. These are type of T-lymphocyte (white blood cells) that help coordinate immune system's response to infection and disease. They use a molecule called CD4 on their surface to detect foreign substances. HIV-1 infects the $CD4^+$ T cells through first binding to the receptors on $CD4^+$ T cells. This phase in which the virus begins to replicate is known to be acute infection. The rapid replication of the virus causes the reduction in $CD4^+$ T cells.

Despite the robust response of immune system and initiation of treatment (HAART) by an infected individual, HIV-1 still persist in an infectious state. The challenge to curing HIV infection lies on the power of HIV to patiently wait in the infected subject before it makes more copies of itself. This virus rest in $CD4^+$ T cells to develop latent reservoirs that are usually established a few days after the duration of the HIV-1 infection. The challenge to eradication of the virus in an infected individual, lies in the clearing of the latent reservoirs. In recent studies, it has been shown that the eradication of the virus can be achieved through reactivation of latent HIV-1.

The latent reservoir is established a few days after a duration of infection on an infected individual [6, 7]. In the study by Williams S. A. et al. [6],

these latently infected cells are then activated due to exposure of their cellular host to selected cytokines, and they continue repopulating during active viral replication. The long-lived cells persist regardless of antiviral therapy consumed by an infected individual [8], hence the long-term use of the antiviral therapy has failed to eradicate the virus in an infected individual [7]. The failure of HAART to cure HIV-1, lies in the latently infected $CD4^+$ T cells, that provide a reservoir for HIV-1. HAART only keeps the HIV-1 infection to a chronic infectious stage, which implies that it only inhibits the initiation of new infection cycle of the virus produced from cellular reservoir [8]. Thus, clearing of latent reservoir is of interest in inventing strategies that will completely eradicate the virus from an infected individual.

The latent state of infection result from the fact that some activated $CD4^+$ T cell reverse the state of virus replication to return to resting state and persist as memory cells [9]. These cells will only produce the virus when they are activated, hence when they are in latent state, they wait patiently and undetectable even by HAART for a chance to reproduce. The long life span and slow decay rate of the latent $CD4^+$ T cells guarantees lifetime persistence of these cells [9, 10]. Thus there must exist factors that influence activation of these cells. Lassen K et al. [9], state that the resting cells lack the sufficient level of HIV-1 Tat and Tat-associate activation-dependent host factor that are necessary for processive transcription.

Recently, it has been discovered that it is not only the T-cells that drive the dynamics of HIV-1 but also the existence of the protein called Tat. According

to the Salk team (2014), HIV-1 cannot live without the existence of Tat. The Tat protein serves as a HIV-1 scout for suitable environment for the virus to replicate [18]. As a result when the environment has been discovered, only then it kicks off the HIV's transcription to enable the virus to replicate and spread [18]. In a recent study by Chen Y. et al. [23], a protein named Ssu72 was demonstrated to play a key role through interacting with Tat, in activation of the resting virus, by binding directly to Tat and also building a feedback loop to speed up the process of replication [18].

1.2 Research question

What is the effect of Tat and Ssu72 on the activation of latently infected CD4⁺ T cells and on the response of immune system?

1.3 Problem statement

The recent discovery of Ssu72 protein by Chen Y. et al. [23], known to be a partner to Tat protein is assumed to play a key role in activation and replication of HIV-1. It is assumed that the interplay between the two proteins might play a crucial role in activating the latently CD4⁺ T cells. In this study we look at the contribution of the two proteins in the dynamics of HIV, specifically the resting virus in CD4⁺ T cells, whether the two proteins enhance the activation of latent virus or not. The study of these proteins might play a critical role in the integration of treatment.

1.4 Aim

The aim of this study is to investigate if the activation of latently infected $CD4^+$ T cells by Tat and Ssu72 clears the latent reservoirs through the immune response.

1.5 Objectives

1. To use the in-host model to capture the dynamics of HIV infection. We shall capture the dynamics of Tat and Ssu72 using a mutualistic system of two equations.
2. To use the in-host HIV infection model with a constant virus production, incorporated with the dynamics of Tat and Ssu72 to capture and analyze the effects of the two proteins on latently infected $CD4^+$ T cells.
3. To use mathematical theories and spectral based methods to analyze the in-host HIV infection model with constant virus production incorporated with Tat and Ssu72.

1.6 Significance of the study

The importance of this study is understanding the impact of Tat and Ssu72 proteins on the persistent HIV-1 infection as well as the influence of Tat and Ssu72 proteins on the activation of the latent HIV-1 and replication of the virus. This study might possibly lead to the development of better strategies

against HIV-1. The study will pave a way for future studies aimed to modify intervention strategies to eradication of HIV-1 infection in an infected subject.

1.7 Scope of the study

In this chapter we have discussed the background of the study, presented a research question, problem statement, aim and objectives, and the significance of the study. The rest of the dissertation is organized as follows. Chapter 2 presents a literature review of the topic, we first give the introduction of HIV-1 infection dynamics, a brief description of Tat and Ssu72 proteins and a brief discussion on preliminaries. In chapter 3 we formulate and analyze the HIV-1 model with a constant virus, followed by the HIV-1 model incorporating Tat and Ssu72 proteins in chapter 4. In chapter 5 we present and discuss numerical results of the two model as well as conclusions.

Chapter 2

Literature Review

2.1 Introduction of HIV-1 infection dynamics

Human Immunodeficiency type 1 (HIV-1) is a virus that infect and weakens the human immune system and $CD4^+$ T cells are the main target of this virus. Hence, HIV-1 infection is characterized by the absence of HIV-1 specific $CD4^+$ T helper cell responses, and in turn resulting in disease progression [11]. F. Chirove and E. Lungu (2013), mentioned that matured HIV particles inside actively infectious $CD4^+$ T cell leave the cell through budding or by lysing the host cell to infect more targets. This process produces more viral particles which continues to fight immune response and finally defeating the immune system. Without treatment, HIV infection can progressively result in a deadly stage of Acquired Immunodeficiency syndrome (AIDS). HIV/AIDS infection is characterized by four basic stages, namely, seroconversion and primary HIV infection, chronic HIV infection, the pre-AIDS stage, and the AIDS stage [3, 19].

T-cells are type of white blood cells that play an important role in the body's immune system [13]. These type of cells develop from liver or bone marrow stem cells that mature in the thymus [16]. These cells play a major role in cell mediated immunity. They contain protein called T-cell receptors that populate the cell membrane [15]. These receptors are capable of recognizing various types of antigens. There exist three primary classes of T-cells that play specific role in the destruction of antigens, namely, cytotoxic T cells, helper T cells and regulatory T cells [15]. There are two main types of T-cell which are of interest in the dynamics of HIV-1, namely, $CD4^+$ T and $CD8^+$ T cells. $CD4^+$ T cells have the glyco-protein called CD4 on their surface [16]. These cells are known to be the helper cells and to initialize the body's response to infection. Where as $CD8^+$ T cells have a glyco-protein called CD8 on their surface [16]. $CD8^+$ T cells are known to be killer cells, and they produce antiviral substances (antibodies) that help fight off the foreign invader.

According to Altfeld and Rosenberg (2000), antigen-specific $CD4^+$ T cell play a vital role in control of chronic viral infection. The critical importance of $CD4^+$ T helper cell responses is maintaining cytotoxic T lymphocyte (CTL) function. $CD4^+$ T cells play a critical role in maintenance of CTL responses during the chronic phase of infection. In the absence of sufficient $CD4^+$ T cells help, antiviral CTLs persist in an inactive state. Hence, $CD4^+$ T helper cell and $CD8^+$ cytotoxic T cell responses are essential for the maintenance of effective immunity in chronic viral infections.

A number of HIV models only account for the acute and asymptomatic latency phase and cannot explain the progression to AIDS [28]. S. Alizon and C. Magnus (2012) review a few number of HIV models and discuss the robustness of the biological hypotheses of these models. The hypotheses of interest were; virus diversity, loss of immune cells, phenotypic switches. They found that the advance models compared to basic models gave more information to test hypotheses that can explain the onset of AIDS [28]. However, amongst these methods, they failed to find (understand) factors that lead to the onset of AIDS. Though a vast numbers of HIV model (played a vital role in treatment development) have been established, but Perelson et al. [28] suggest a need of models explaining the whole dynamics of HIV infection.

F. Chirove and E. Lungu (2013), studied the one strain model of HIV infection by looking at the cell-free infection mechanism under the assumption of constant viral production and density dependent viral product mechanism. The treatment was imposed on the cell-to-cell infection mechanism. Through the use of mathematical techniques, conclusion were taken regarding the effects of treatment on the cell-to-cell mechanism, and the incorporation of a constant and density dependent viral production. The benefit of initiation of treatment before the threshold of developed AIDS ($CD4^+$ T cell count $< 200 \text{ mm}^{-3}$) were shown. Amongst these benefits, they mention, the restoration of immune system's strength, depletion of viral production to undetectable levels and reduction of severity of the infection.

A. S. Perelson and R. M. Ribero (2013), review development of HIV modeling, emphasizing qualitative findings about HIV biology uncovered by studying acute infection, the response to drug therapy and the rate of generation of HIV variant that escape immune response. They mention factors that contribute in progression of the infection (even for patients in ARVs), which are, latent reservoirs and drug resistance. They also mention factors that contribute to resistance and the diversity of HIV, which are, high rate of mutation of virus, its fast life cycle and the long-term nature of HIV infection. In their study they suggest that development of a vaccine that prevents infection in the first course of disease is very important.

2.2 HIV-1 Tat

Trans-Activating Transcription (Tat) is a regulatory protein produced very early after the HIV infection, necessary for viral gene expression, cell-to-cell virus transmission and disease progression and can be released extracellularly by leaderless secretory path, even during anti-retro-viral therapy [24, 25]. According to Lassen K. et al. [9], Tat is synthesized early after a subset of multiply joined viral RNA species. Tat is essential for HIV-1 replication. According to Watson and Edwards (1999), during the initial phase of infection, large amounts of Tat, together with other regulatory protein, are synthesized and drive HIV-1 replication [24]. Tat has a remarkable property, it can leave cells from which it is synthesized and cross the cell membrane of adjacent cells, where it localizes in the nucleus [24].

Tat maintains its activity and, once inside the nucleus, is able to trans-activate a number of genes, especially those relating to cytokine production, and thus can modulate certain cellular activities [24]. These cellular activities are viral gene expression. Tat achieves this process through binding with RNA, acting as a level of elongation [9]. Tat is a potent trans-activator of HIV-1, and is also able to trans-activate other genes. Trans-activation by Tat is entirely dependent upon the presence of TAR RNA, a transcription control element that appears to be unique to lentiviruses [24]. Extracellular Tat leaves the host cell to enter the adjacent cells, resulting in the activation of resting cell, suggesting that Tat plays an important role in the chronic immune activation present during the HIV infection. According to Nicoli F. et al. [25], Tat is shown to play a vital role in the proliferation of CD8⁺ T cells.

2.3 Ssu72 Protein

The protein Ssu72 also plays a crucial role in speeding up the process of HIV-1 replication. It is essential for Tat:P-TEFb-mediated phosphorylation of the S5P-CTD [23]. Ssu72 also stimulates nascent HIV-1 transcription in phosphate dependent manner by synergizing with Tat in a phosphate dependent manner to activate transcriptional from integrated HIV-1. The interaction between the two proteins can be thought as Tat being an engine for HIV replication and Ssu72 revs up the engine [18].

The knock down of Ssu72 impairs Tat transcription. Due to a fact that Ssu72

is recruited by Tat to the integrated HIV-1 proviral promoter in TNF- α , and also the direct interaction between Tat and Ssu72 which strongly stimulates Tat CTD phosphate activity [23]. The important role of Ssu72 is through binding to Tat which not only activates the transcription, but also builds the feedback loop to speed up the the process. Unlike the protein CycT1 (Tat's partner), Ssu72 is not commonly required for cellular gene transcription, which makes it a useful target to selectively disrupt viral gene expression in infected cells [18].

Most trusted methods for numerical simulation in analysis of initial value problems (IVP) have been MatLab ode solvers such as, ode45, ode113 and ode23. Recently, Motsa et al. [40, 41, 42] have shown an interest in developing spectral based methods, to solve chaotic systems, such as, Lorenz, Chen and Rikitake. In 2012 they presented a multistage successive linearisation method (MSLM) which was super succeeded by the multistage spectral relaxation method (MSRM). These methods solve large interval IVPs by dividing the interval into small sub-intervals. In this study we apply the MSRM to solve the model incorporating Tat and Ssu72. The MSRM was found to be reliable and accurate through the comparison with built-in MatLab based ode45 solver [40, 42].

2.4 Preliminaries

2.4.1 Existence of solutions [29]

Consider

$$\dot{y}_m = f_m(t, y_1, \dots, y_n), \text{ with } m = 1, \dots, n \quad (2.1)$$

subject to initial conditions $y_m = y_{m0}$ and $t = t_0$. The region D (a parallelepiped in $n + 1$ dimension) is defined by $t_0 \leq t \leq t_0 + h$, $|y_m - y_{m0}| \leq k_m$ ($m = 1, \dots, n$) where $h < k_m/M$, M being bound for f_m , i.e $|f| < M$.

Theorem 2.4.1. *{Existence Theorem}: Let $f_m(t, y_1, \dots, y_n)$ be a single-valued continuous function of t, y_1, \dots, y_n in D such that for $m = 1, \dots, n$*

$$(a) |f_m(t, y_1, \dots, y_n)| < M \text{ in } D$$

$$(b) \text{ (**Lipschitz condition**)}$$

$$|f_m(t, y_1, \dots, y_n) - f_m(t, y'_1, \dots, y'_n)| < K_1|y_1 - y'_1| + \dots + K_n|y_n - y'_n|,$$

K_1, \dots, K_n being finite constants, for any (t, y_1, \dots, y_n) and (t, y'_1, \dots, y'_n) in D . Then, for $h < k_m/M$ ($m = 1, \dots, n$), the system (2.1) possesses one and only one set of continuous solution $y_1(t), \dots, y_n(t)$ in $t_0 \leq t \leq t_0 + h$ such that $y_m(t_0) = y_{m0}$ ($m = 1, \dots, n$).

2.4.2 Equilibrium state [29]

Consider a nonlinear dynamical system

$$\dot{y} = f(t, y), \quad y \in \mathbb{R}^m. \quad (2.2)$$

Definition 2.4.1. $a \in \mathbb{R}^m$ is an equilibrium state for (2.2) if $f(t, a) = 0$, for all t .

Remark. If the dynamical system is initialised at an equilibrium state, then it stays there, that is, if $x(t_0) = a$, then $x(t) = a$ for all $t \geq t_0$.

2.4.3 Stability [29]

Definition 2.4.2. An equilibrium state $x^* = a$ is said to be:

- (a) **Stable** if for any positive scalar ϵ there exist a positive scalar σ such that $\|x(t_0)\| < \sigma$, $\|x(t)\| < \epsilon$ for all $t \geq t_0$,
- (b) **Asymptotically stable** if it is stable and if in addition $x(t) \rightarrow x^*$ as $t \rightarrow \infty$,
- (c) **Unstable** if it not stable, that is, there exist an $\epsilon > 0$ such that for every $\sigma > 0$ there exist an $x(t_0)$ with $\|x(t_0)\| < \sigma$, $\|x(t_1)\| \geq \epsilon$ for some $t_1 > t_0$.

There exist several method that can be use to analyse the stability of an equilibrium state, namely, Liapunov function, center manifold theory, Jacobian (eigenvalue) and Routh Hurwitz stability criterion.

2.4.4 Center manifold theorem [31]

Theorem 2.4.2. Consider the following general system of ordinary differential equations with a parameter ϕ_a

$$\frac{dx}{dt} = f(x, \phi_a), \quad f : \mathbb{R}^n \times \mathbb{R} \rightarrow \mathbb{R} \text{ and } f \in \mathbb{C}^2(\mathbb{R}^n \times \mathbb{R}). \quad (2.3)$$

Without loss of generality, it is assumed that 0 is an equilibrium for system (2.3) for all values of the bifurcation parameter ϕ_a , that is $f(0, \phi_a) = 0$ for all ϕ_a and we assume

- $A = D_x f_l(0, \phi_a^*) = \left(\frac{\partial f_l}{\partial x_q}(0, \phi_a^*) \right)$ is the linearization of the system (2.3) around 0 with ϕ_a evaluated at ϕ_a^* . Zero is a simple eigenvalue of A and the eigenvalues of A have negative real part.
- Matrix A has a right eigenvector w and a left eigenvector v corresponding to the zero eigenvalue.

The local dynamics of (2.3) around 0 are totally governed by a and b , where a and b are given by

$$\begin{aligned} a &= \sum_{l,p,q}^n v_l w_p w_q \frac{\partial^2 f_l}{\partial x_p \partial x_q}, \\ b &= \sum_{l,p}^n v_l w_p \frac{\partial^2 f_l}{\partial x_p \partial \phi_a^*}. \end{aligned} \tag{2.4}$$

Therefore

1. $a > 0$, $b > 0$. When $\phi_a < 0$ with $|\phi_a| \ll 1$, 0 is locally asymptotically stable, and there exists a positive unstable equilibrium; when $0 < \phi_a \ll 1$, 0 is unstable and there exists a negative and locally asymptotically stable equilibrium;
2. $a < 0$, $b < 0$. When $\phi_a < 0$ with $|\phi_a| \ll 1$, 0 is unstable; when $0 < \phi_a \ll 1$, 0 is locally asymptotically stable, and there exists a positive unstable equilibrium;
3. $a > 0$, $b < 0$. When $\phi_a < 0$ with $|\phi_a| \ll 1$, 0 is unstable, and there exists a locally asymptotically stable negative equilibrium; when $0 < \phi_a \ll 1$, 0 is stable, and a positive unstable equilibrium appears;

4. $a < 0$, $b > 0$. When ϕ_a changes from negative to positive, 0 changes its stability from stable to unstable. Correspondingly a negative unstable equilibrium becomes positive and locally asymptotically stable.

2.4.5 Descartes rule of signs [30]

The Descartes' rule of signs is a method for finding the number of roots and signs of the real roots of a polynomial function.

Let

$$P(x) = \sum_{k=0}^n a_k x^{n-k}, \quad k = 0, 1, \dots, n \quad (2.5)$$

be a polynomial function of order n and a_k are real constant. The function $P(x)$ has n complex solutions thanks to the fundamental theorem of algebra. Then the general concept regarding Descartes' rule of signs for finding signs of roots is given as follows,

- The number of positive real zeros of P is either equal to the number of variations in sign of $P(x)$ or less than this by an even number.
- The number of negative real zeros of P is either equal to the number of variation in sign of $P(-x)$ or less than this by an even number.

Chapter 3

HIV-1 model with a constant virus production

3.1 Introduction

In this chapter we formulate and analyze the model with a constant virus production. This model shall capture the dynamics of five classes of HIV-1. We use analytic strategies such as feasible region, equilibrium points and stability analysis to study the behavior of the model.

3.2 Model formulation

In this study we extend one strain model with constant virus production [17], to incorporate the role of trans-activating transcription (Tat), T_a , and Ssu72, S_u on the dynamic of HIV-1. The constant virus production model consist of five classes , namely, uninfected $CD4^+$ T cells population, T , la-

tently infected CD4⁺ T cells population, I_L , active infected CD4⁺ T cells population, I_A , virus population, V_I , and the CD8⁺ T cells population, Z . The two proteins to be incorporated have been shown to play a vital role in activation of latently infected cells and replication of HIV-1.

We assume that recruited CD4⁺ T cells from the thymus enter the T class at a constant rate π and die naturally at a constant rate μ . The CD4⁺ T cells can be infected with the virus at a constant rate β . Thus the rate of change of CD4⁺ T cells is given by

$$\frac{dT}{dt} = \pi - \mu T - \beta TV_I. \quad (3.1)$$

Throughout the infectious phase not all CD4⁺ T cells are actively infectious. Some CD4⁺ T cell will at this stage be latently infected and some will be actively infectious. Thus, a proportion α of infected cells become latently infected and $(1 - \alpha)$ become actively infectious. The latently infected cells can be activated into actively infectious cells at a constant rate γ and die naturally at a constant rate μ . Thus the rate of change of latently infected CD4⁺ T cells population is given by

$$\frac{dI_L}{dt} = \alpha \beta TV_I - (\mu + \gamma) I_L. \quad (3.2)$$

The actively infectious CD4⁺ T cells die naturally at a constant rate μ and die at a constant rate, ω , due to lysis caused by the virus. The actively infectious CD4⁺ T cell also die at a constant rate σ due to the killing by CD8⁺ T cells. The rate of change of actively infectious CD4⁺ T cells population is given by

$$\frac{dI_A}{dt} = (1 - \alpha) \beta TV_I + \gamma I_L - (\mu + \omega) I_A - \sigma I_A Z. \quad (3.3)$$

We assume that each actively infectious $CD4^+$ T cell produces an average of N viral particles. The viral particles produced by these cells occur at a rate ωNI_A . μ_v is the death rate of the virus. The rate of change of virus is given by

$$\frac{dV}{dt} = \omega NI_A - \mu_v V. \quad (3.4)$$

We suppose that $CD8^+$ T cells are recruited from thymus at a constant rate of π_1 and die naturally at a rate μ_1 . The $CD8^+$ T cells are also produced proportionally to the presence of infected $CD4^+$ T cells at a rate β_1 . The rate of change of $CD8^+$ T cells is then given by

$$\frac{dZ}{dt} = \pi_1 + \beta_1 I_A - \mu_1 Z. \quad (3.5)$$

The in-host dynamics of the HIV infection is represented by the model diagram shown in Figure 3.1

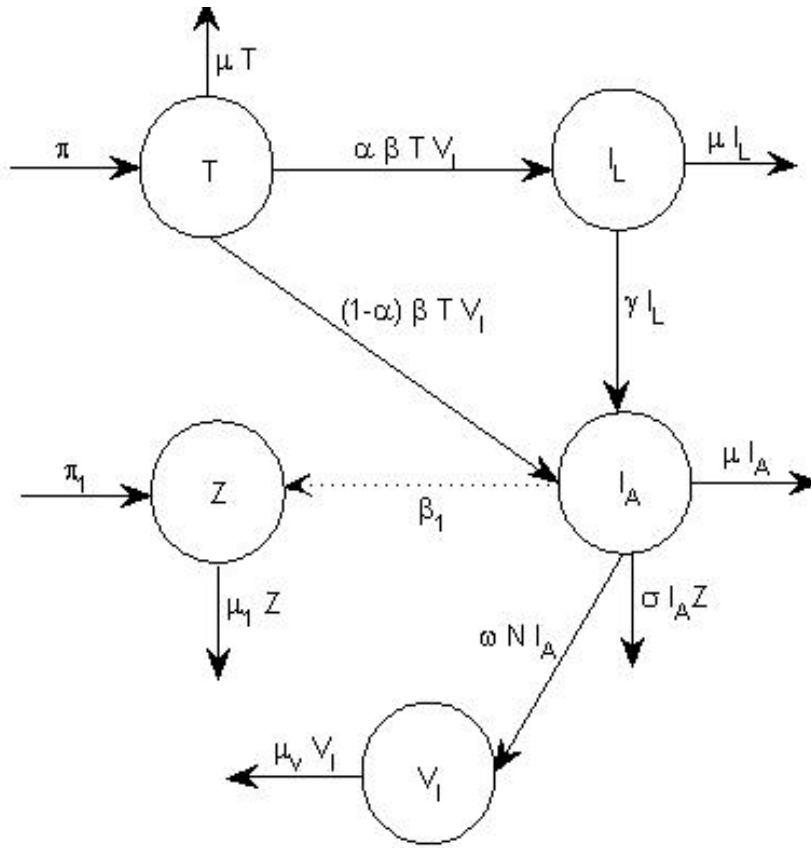


Figure 3.1: Model showing the interaction of the compartments

3.3 Feasible region of the model

We proceed to analyse the behavior of the model constructed in section 3.2. We shall determine the existence of solutions, calculate the equilibrium points, calculate the basic reproduction number and carry out stability analysis of equilibrium point in our model analysis.

For analysis of the model, we need to have a feasible region, where the model will be biological meaningful. We denote the feasible region by Λ_0 and define it so that it will be positively invariant. The positive invariance ensures that the positive solutions are both mathematically and biologically meaningful. Thus, the population considered in the system of equations (3.1)-(3.5) are cells, whose solutions should always be non-negative. The feasible region is defined by

$$\Lambda_0 = \left\{ (T, I_L, I_A, V_I, Z) \in \mathbb{R}_+^5; T_t < \frac{\pi}{\mu}, V_I \leq \frac{\omega N \pi}{\mu \mu_v} \text{ and } Z < \frac{\mu \pi_1 + \beta \pi}{\mu \mu_1} \right\} \quad (3.6)$$

with initial conditions

$$T(0) > 0, I_L(0) \geq 0, I_A(0) \geq 0, V_I(0) \geq 0 \text{ and } Z(0) > 0. \quad (3.7)$$

Theorem 3.3.1. *The feasible region Λ_0 with initial conditions (3.7) is positively invariant.*

Lemma 3.3.2. *If $T(0) > 0, I_L(0) \geq 0, I_A(0) \geq 0, V_I(0) \geq 0$ and $Z(0) > 0$ then $T(t) > 0, I_L(t) \geq 0, I_A(t) \geq 0, V_I(t) \geq 0$ and $Z(t) > 0$.*

Proof. First we show that the solutions of systems of equations (3.1)-(3.5) are positive. We proceed by contradiction (proof by contradiction). Assume that $\exists t_1 < t$ such that $T(t) \leq 0, I_L(t) \geq 0, I_A(t) \geq 0, V_I(t) \geq 0$ and $Z(t) > 0$. Let $T(t_1) = 0$ first,

Then (3.1) becomes

$$\dot{T} = \pi, \quad (3.8)$$

$$\Rightarrow T(t) = \pi(t - t_1). \quad (3.9)$$

Thus, $T(t) > 0$, $\forall t_1 < t$ which contradicts our assumption. Therefore, there exist no $T(t) \leq 0 \forall t_1 < t$. Hence, Lemma 3.3.2 is true.

Now, (3.2) becomes

$$\dot{I}_L = -(\mu + \gamma)I_L, \quad T(t_1) = 0, \quad (3.10)$$

$$\Rightarrow I_L(t) = I_L(t_1)e^{-(\mu+\gamma)(t-t_1)} > 0, \quad \forall t_1 < t. \quad (3.11)$$

In the same manner it can be shown that when $T(t_1) = 0$, (3.3)-(3.5) become;

$$I_A(t) = \frac{\gamma I_L}{\mu + \omega + \sigma Z} (1 - e^{-(\mu+\omega+\sigma Z)(t-t_1)}) + I_A(t_1)e^{-(\mu+\omega+\sigma Z)t}, \quad (3.12)$$

$$V_I(t) = \omega N I_A (1 - e^{-\mu_v(t-t_1)}) + V_I(t_1)e^{-\mu_v(t-t_1)}, \quad (3.13)$$

$$Z(t) = (\pi_1 + \beta_1 I_A) (1 - e^{-\mu_1(t-t_1)}) + Z(t_1)e^{-\mu_1(t-t_1)}. \quad (3.14)$$

Thus (3.12)-(3.14) are all non-negative $\forall t_1 < t$ provided $I_A(t_1) > 0$, $V_I(t_1) > 0$, $Z(t_1) > 0$, respectively. The same can be done for the cases where we choose at least one of the state variables at time t_1 to be negative. The similar conclusion is reached, that is, the solutions for (3.1)-(3.5) remain in the positive region $\forall t$ with respect to non-negative initial conditions, i.e., (3.7). Thus, the Lemma 3.3.2 is true.

Lastly, we show that the solutions have an upper bound. Let $T_t = T + I_L + I_A$ such that $T_t(0) > 0$. Then

$$\begin{aligned}
\frac{dT_t}{dt} &= \frac{dT}{dt} + \frac{dI_L}{dt} + \frac{dI_A}{dt}, \\
&= \pi - \mu(T + I_L + I_A) - \omega I_A - \sigma I_A Z, \\
&\leq \pi - \mu T_t.
\end{aligned} \tag{3.15}$$

Whose solution are

$$T_t(t) \leq \left(T_t(0) - \frac{\pi}{\mu}\right) e^{-\mu t} + \frac{\pi}{\mu}. \tag{3.16}$$

$$\therefore \limsup_{t \rightarrow \infty} T_t(t) \leq \frac{\pi}{\mu}. \tag{3.17}$$

The population of T_t cannot exceed the value $\frac{\pi}{\mu}$, hence the population T_t is bounded. This means that $T(t) \leq \frac{\pi}{\mu}$, $I_L(t) \leq \frac{\pi}{\mu}$ and $I_A(t) \leq \frac{\pi}{\mu}$.

By the boundedness of I_A ,

$$\omega N I_A \leq \omega N \frac{\pi}{\mu}, \tag{3.18}$$

$$\Rightarrow \omega N I_A - \mu_v V_I \leq \omega N \frac{\pi}{\mu} - \mu_v V_I. \tag{3.19}$$

$$\therefore \frac{dV_I}{dt} \leq \omega N \frac{\pi}{\mu} - \mu_v V_I. \tag{3.20}$$

The solutions for (3.20) are given by

$$V_I \leq \left(V_I(0) + \frac{\omega N \pi}{\mu \mu_v}\right) e^{-\mu_v t} + \frac{\omega N \pi}{\mu \mu_v}. \tag{3.21}$$

$$\therefore \limsup_{t \rightarrow \infty} V_I(t) \leq \frac{\omega N \pi}{\mu \mu_v}. \tag{3.22}$$

Hence, $V_I \leq \frac{\omega N \pi}{\mu \mu_v}$.

Using the same approach above it can be shown that

$$\frac{dZ}{dt} \leq \pi_1 + \beta_1 \frac{\pi}{\mu} - \mu Z. \quad (3.23)$$

Equation (3.23) can be solved to give

$$Z \leq \left(Z(0) + \frac{\mu\pi_1 + \beta\pi}{\mu\mu_1} \right) e^{-\mu_1 t} + \frac{\mu\pi_1 + \beta\pi}{\mu\mu_1}. \quad (3.24)$$

Thus,

$$\limsup_{t \rightarrow \infty} Z \leq \frac{\mu\pi_1 + \beta\pi}{\mu\mu_1}. \quad (3.25)$$

Hence, the solutions of Z have an upper bound $\frac{\mu\pi_1 + \beta\pi}{\mu\mu_1}$.

Since the solutions of (3.1)-(3.5) are positive and bounded, therefore we conclude that the feasible region Λ_0 with initial conditions, (3.7), is positively invariant. \square

3.3.1 Disease free equilibrium point

The disease free equilibrium point (DFE) is the state in which there exist no infection. To obtain this state in our model, we set $V^* = 0$, $I_L^* = 0$, and $I_A^* = 0$ to obtain

$$E_{10} = \left(\frac{\pi}{\mu}, 0, 0, 0, \frac{\pi_1}{\mu_1} \right). \quad (3.26)$$

In the next subsection 3.3.2 we introduce the concept of the basic reproduction number and the use of it.

3.3.2 Basic reproduction number

The basic reproduction number, R_0 , is referred to as the expected number of secondary infections produced by an index case in a completely susceptible

population [32, 33]. In an in-host dynamics, R_0 gives the number of newly infected cells produced by one infected cell during its lifetime, assuming all other cells are susceptible [32]. It follows then that, if $R_0 < 1$, then a few infected individuals introduced into a completely susceptible population will, on average fail to replicate themselves, and the disease will not spread [34]. If $R_0 > 1$, then the number of infected $CD4^+$ T cells will increase with each generation and the disease will spread [34].

The derivation of the basic reproduction number is based on the linearization of the ODE model about a disease free equilibrium [34]. There are five assumptions based on the construction of R_0 , see [33, 34]. The basic reproduction number is defined mathematically as the spectral radius of the next generation matrix $C = FV^{-1}$ denoted as

$$R_0 = \rho(C), \quad (3.27)$$

where F denotes the $(n \times n)$ matrix of secondary (new) infection and V denotes an $(n \times n)$ matrix of disease progression, death and recovery [34]. In general R_0 is an eigenvalue of C and is strictly larger in modulus than all other eigenvalues of C [33, 34].

To calculate the basic reproduction number, we identify the infected classes and from those infected classes we extract \mathcal{F} and \mathcal{V} . Now, from equations (3.1)-(3.5), we extract the infected classes I_L , I_A and V_I , such that;

$$\mathcal{F} = \begin{pmatrix} \alpha\beta TV_I \\ (1-\alpha)\beta TV_I \\ 0 \end{pmatrix}, \quad \mathcal{V} = \begin{pmatrix} (\mu + \gamma)I_L \\ -\gamma I_L + (\mu + \omega)I_A + \sigma I_A Z \\ -\omega N I_A + \mu_v V_I \end{pmatrix}. \quad (3.28)$$

The Jacobian of the matrices \mathcal{F} and \mathcal{V} respectively, are obtained to be

$$F = \frac{\partial \mathcal{F}}{\partial x_i} = \begin{pmatrix} 0 & 0 & \alpha\beta T_0 \\ 0 & 0 & (1-\alpha)\beta T_0 \\ 0 & 0 & 0 \end{pmatrix}, \quad V = \frac{\partial \mathcal{V}}{\partial x_i} = \begin{pmatrix} \mu + \gamma & 0 & 0 \\ -\gamma & \mu + \omega + \sigma Z_0 & 0 \\ 0 & -\omega N & \mu_v \end{pmatrix}. \quad (3.29)$$

The inverse of V is,

$$V^{-1} = \begin{pmatrix} \frac{1}{\mu + \gamma} & 0 & 0 \\ \frac{\gamma}{(\mu + \gamma)(\mu + \omega + \sigma Z_0)} & \frac{1}{(\mu + \omega + \sigma Z_0)} & 0 \\ \frac{\gamma\omega N}{\mu_v(\mu + \gamma)(\mu + \omega + \sigma Z_0)} & \frac{\omega N}{\mu_v(\mu + \omega + \sigma Z_0)} & \frac{1}{\mu_v} \end{pmatrix}. \quad (3.30)$$

The next generation matrix is given by

$$FV^{-1} = \begin{pmatrix} \alpha a_1 & \alpha a_2 & \alpha a_3 \\ (1-\alpha)a_1 & (1-\alpha)a_2 & (1-\alpha)a_3 \\ 0 & 0 & 0 \end{pmatrix}, \quad (3.31)$$

where $T_0 = \frac{\pi}{\mu}$, $Z_0 = \frac{\pi_1}{\mu_1}$, $a_1 = \frac{\beta\gamma\omega NT_0}{\mu_v(\mu + \gamma)(\mu + \omega + \sigma Z_0)}$, $a_2 = \frac{\beta\omega NT_0}{\mu_v(\mu + \omega + \sigma Z_0)}$ and $a_3 = \frac{\beta T_0}{\mu_v}$.

The basic reproduction number, which is defined as the spectral radius of the next generation matrix FV^{-1} can be determined as follows. The three eigenvalues of the matrix FV^{-1} are

$$\lambda_{0,1} = 0, \text{ and } \lambda_2 = \frac{\gamma\alpha\omega N\beta T_0}{\mu_v(\mu + \gamma)(\mu + \omega + \sigma Z_0)} + \frac{(1-\alpha)\omega N\beta T_0}{\mu_v(\mu + \omega + \sigma Z_0)}. \quad (3.32)$$

λ_2 is the largest eigenvalue and hence, the reproduction number is given by

$$R_0 = \frac{\gamma\alpha\omega N\beta T_0}{\mu_v(\mu + \gamma)(\mu + \omega + \sigma Z_0)} + \frac{(1-\alpha)\omega N\beta T_0}{\mu_v(\mu + \omega + \sigma Z_0)}. \quad (3.33)$$

The numerator on the reproduction number is composed of the rates in which the infection keeps persisting, i.e, the rate of activation of latently infected cells to be actively infectious and the rate at which the virus is produced. Where as the denominator is composed by the rates of death of cells and infection.

3.4 Endemic equilibrium point

To attain the endemic equilibrium points we set the right hand side of the system of equations (3.1)-(3.5) to zero.

$$\pi - \mu T^* - \beta T^* V_I^* = 0, \quad (3.34)$$

$$\alpha \beta T^* V_I^* - (\mu + \gamma) I_L^* = 0, \quad (3.35)$$

$$(1 - \alpha) \beta T^* V_I^* + \gamma I_L^* - (\mu + \omega) I_A^* - \sigma I_A^* Z^* = 0, \quad (3.36)$$

$$\omega N I_A^* - \mu_v V_I^* = 0, \quad (3.37)$$

$$\pi_1 + \beta_1 I_A^* - \mu_1 Z^* = 0. \quad (3.38)$$

Using equations (3.35) and (3.37) we rewrite equation (3.36) in terms of I_A^* and T^* , which yields,

$$\left(\frac{(1 - \alpha) \beta \phi N T^*}{\mu_v} + \frac{\gamma \alpha \beta \omega N T^*}{\mu_v (\mu + \gamma)} - (\mu + \omega + \sigma Z^*) \right) I_A^* = 0. \quad (3.39)$$

The resulting solutions from (3.39) are,

$$I_A^* = 0, \text{ and } T^* = \frac{\mu_v (\mu + \gamma) (\mu + \omega + \sigma Z^*)}{\omega \beta N [(1 - \alpha) (\mu + \gamma) + \alpha \gamma]}.$$

Note that when $I_A^* = 0$ we obtain the disease free equilibrium point. Therefore, the endemic equilibrium point will be given by T^* . Since from (3.38)

$$Z^* = Z_0 + \frac{\beta_1}{\mu_1} I_A^* \quad (3.40)$$

then T^* can be rewritten in terms of I_A^* and R_0 as

$$T^* = \frac{T_0}{R_0} + A \frac{\sigma\beta_1}{\mu_1} I_A^*, \quad (3.41)$$

with $A = \frac{\mu_v(\mu + \gamma)}{\omega\beta N[(1 - \alpha)(\mu + \gamma) + \alpha\gamma]}$. Therefore, I_L^* and V_I^* in terms of I_A^* are given by

$$I_L^* = \frac{BT_0}{R_0} I_A^* + \frac{\sigma\beta_1}{\mu_1} A B I_A^{*2}, \quad (3.42)$$

$$V_I^* = \frac{\omega N I_A^*}{\mu_v}, \quad (3.43)$$

with $B = \frac{\alpha\omega N\beta}{\mu_v(\mu + \gamma)}$. If we now substitute, T^* and V_I^* into (3.34) to solve for I_A^* , we obtain a quadratic equation, given by

$$I_A^{*2} + \left(\frac{A\sigma\beta_1\mu}{\mu_1} + \frac{\omega N\beta T_0}{\mu_v R_0} \right) \frac{\mu\mu_v}{A\sigma\omega N\beta\beta_1} I_A^* - \frac{\mu\mu_v}{A\sigma\omega N\beta\beta_1} \frac{\pi}{R_0} (R_0 - 1) = 0. \quad (3.44)$$

To solve for I_A^* we consider the following three cases for which we must attain a positive solution for an endemic equilibrium point.

Theorem 3.4.1. *The endemic equilibrium point E_{11} exists only when $R_0 > 1$.*

Proof. Consider the following cases

Case 1: $R_0 < 1$

If $R_0 < 1$, then by the Descartes' rule of signs, (3.44) have two negative real roots. Since the two roots have no biological meaning, then we disregard the case where $R_0 < 1$ for the existence of positive solution.

Case 2: $R_0 = 1$

When $R_0 = 1$ we have that

$$I_A^* = 0 \text{ or } I_A^* = - \left(\frac{A\sigma\beta_1\mu}{\mu_1} + \frac{\omega N\beta T_0}{\mu_v R_0} \right) \frac{\mu\mu_v}{A\sigma\omega N\beta\beta_1} < 0.$$

We therefore disregard the negative solution.

Case 3: $R_0 > 1$

In this case, by the Descartes' rule of signs, (3.44) we have one positive real root and one negative real root. Since the negative root has no biological meaning and fails the assumption of positive invariant set Λ_0 , it is for this reason that it is disregarded. Thus, I_A^* for an endemic equilibrium is given by the positive root, that is

$$I_A^* = \frac{1}{2} \left(-A_1 + \sqrt{A_1^2 + 4A_2} \right), \quad (3.45)$$

with $A_1 = \left(\frac{A\sigma\beta_1\mu}{\mu_1} + \frac{\omega N\beta T_0}{\mu_v R_0} \right) \frac{\mu\mu_v}{A\sigma\omega N\beta\beta_1}$ and $A_2 = \frac{\mu\mu_v}{A\sigma\omega N\beta\beta_1} \frac{\pi}{R_0} (R_0 - 1)$.

Thus the endemic equilibrium point is given by $E_{11} = (T^*, I_L^*, I_A^*, V_I^*, Z^*)$ where the expressions for T^* , I_L^* , I_A^* , V_I^* , and Z^* are given in equations (3.41), (3.42), (3.45), (3.43), and (3.40), respectively. \square

3.5 Stability analysis of equilibrium points

In this section we analyze the stability of both the disease free and the endemic equilibrium points.

3.5.1 Local stability of DFE

To prove the local stability of the disease free equilibrium point, the Routh-Hurwitz stability criterion method is used. For local stability of DFE, we shall show that all the eigenvalues associated with the DFE are negative.

Theorem 3.5.1. *The disease free equilibrium of the system, (3.1)-(3.5), is locally asymptotically stable if $R_0 < 1$ and unstable when $R_0 > 1$.*

Proof. To find the first three eigenvalues, we use a (3×3) matrix extracted from the Jacobian matrix evaluated at the DFE. Routh-Hurwitz stability criterion is then used to find necessary condition for the eigenvalues to be negative real and for the DFE to be asymptotically stable. The (3×3) matrix is

$$F - V = \begin{bmatrix} -(\mu + \gamma) & 0 & -\frac{\beta\pi}{\mu} \\ \gamma & -(\mu + \omega + \frac{\sigma\pi_1}{\mu_1}) & (1 - \alpha)\frac{\beta\pi}{\mu} \\ 0 & \omega N & -\mu_v \end{bmatrix}. \quad (3.46)$$

The eigenvalues λ of $F - V$ are the solutions of the characteristic polynomial $\det((F - V) - \lambda I) = 0$, where I is the (3×3) identity matrix. This gives

$$\lambda^3 + b_1\lambda^2 + b_2\lambda + b_3 = 0, \quad (3.47)$$

with

$$b_1 = (2\mu + \gamma + \mu_v + \omega + \sigma Z_0),$$

$$b_2 = [(\mu + \gamma + \mu_v)(\mu + \omega + \sigma Z_0) + \mu_v(\mu + \gamma) - (1 - \alpha)\omega\beta NT_0],$$

$$b_3 = \mu_v(\mu + \gamma)(\mu + \omega + \sigma Z_0)(1 - R_0).$$

By the Routh-Hurwitz conditions, equation (3.47) has negative roots if

$$b_1 > 0, \quad b_3 > 0, \quad b_1 b_2 - b_3 > 0.$$

Clearly, $b_1 > 0$ and $b_3 > 0$ when $R_0 < 1$. The condition

$$\begin{aligned} b_1 b_2 - b_3 &= (2\mu + \gamma + \mu_v + \omega + \sigma Z_0)[(\mu + \gamma)(\mu_v + \omega + \sigma Z_0) + \\ &\quad \mu_v(\mu_v + \omega + \sigma Z_0) - (1 - \alpha)\omega\beta NT_0] + \mu_v(\mu + \gamma)[(2\mu + \gamma) + (\mu_v + \omega + \sigma Z_0)R_0] \\ &= (2\mu + \gamma + \mu_v + \omega + \sigma Z_0) \left[(\mu + \gamma)(\mu_v + \omega + \sigma Z_0) + \right. \\ &\quad \mu_v(\mu_v + \omega + \sigma Z_0) \left(1 - \frac{\gamma\alpha\omega N\beta T_0}{\mu_v(\mu + \gamma)(\mu + \omega + \sigma Z_0)} - \frac{(1 - \alpha)\omega N\beta T_0}{\mu_v(\mu + \omega + \sigma Z_0)} + \right. \\ &\quad \left. \left. \frac{\gamma\alpha\omega N\beta T_0}{\mu_v(\mu + \gamma)(\mu + \omega + \sigma Z_0)} \right) \right] + \mu_v(\mu + \gamma)[(2\mu + \gamma) + (\mu_v + \omega + \sigma Z_0)R_0] \\ &= (2\mu + \gamma + \mu_v + \omega + \sigma Z_0) \left[(\mu + \gamma)(\mu_v + \omega + \sigma Z_0) + \right. \\ &\quad \left. \mu_v(\mu_v + \omega + \sigma Z_0)(1 - R_0) + \frac{\gamma\alpha\omega N\beta T_0}{\mu + \gamma} \right] + \\ &\quad \mu_v(\mu + \gamma)[(2\mu + \gamma) + (\mu_v + \omega + \sigma Z_0)R_0] \\ &> 0 \end{aligned}$$

when $R_0 < 1$. Since all the three conditions are satisfied we conclude that the three eigenvalues from a matrix (3.46) are all non-positive.

The other two eigenvalue are

$$\lambda_1 = -\mu < 0, \tag{3.48}$$

$$\lambda_2 = -\mu_1 < 0. \tag{3.49}$$

Hence, by the Routh-Hurwitz criterion the disease equilibrium point is asymptotically stable when $R_0 < 1$. On the other hand when $R_0 > 1$, there exist

one positive root and four negative roots, implying that we have an unstable DFE. \square

3.5.2 Global stability of the DFE

In order to study the global stability of the equilibrium, we use the Lyapunov method. This method seek for a function which shall satisfy some necessary and sufficient conditions, to ensure the global stability of an equilibrium.

Suppose the Lyapunov function, denoted as U is continuously differentiable in the set D , then the necessary and sufficient conditions for global stability of an equilibrium $x^* = \mathbf{0}$ are

1. $U(\mathbf{0}) = 0$
 2. $U > 0, \forall \mathbf{x} \in D - \{\mathbf{0}\}$
 3. $\dot{U} < 0, \forall \mathbf{x} \in D - \{\mathbf{0}\}.$
- (3.50)

Theorem 3.5.2. *The disease free equilibrium is globally stable if $R_0 < 1$.*

Proof. Consider the corresponding Lyapunov function defined as

$$U = \left(T - T_0 - T_0 \ln \frac{T}{T_0} \right) + c_1 I_L + c_2 I_A + c_3 V_I + \left(Z - Z_0 - Z_0 \ln \frac{Z}{Z_0} \right). \quad (3.51)$$

Equation (3.51) by definition is positive definite. Using the chain rule, the derivative of (3.51) is given by

$$\dot{U} = \frac{\partial U}{\partial T} \dot{T} + c_1 \frac{\partial U}{\partial I_L} \dot{I}_L + c_2 \frac{\partial U}{\partial I_A} \dot{I}_A + c_3 \frac{\partial U}{\partial V_I} \dot{V}_I + \frac{\partial U}{\partial Z} \dot{Z}. \quad (3.52)$$

where the dot defines the derivative with respect to time, t . Substituting, \dot{T} , \dot{I}_L , \dot{I}_A , \dot{V}_I , and \dot{Z} into (3.52), we get

$$\begin{aligned} \dot{U} = & \left(1 - \frac{T_0}{T}\right) (\pi - \mu T - \beta TV_I) + c_1(\alpha \beta TV_I - (\mu + \gamma)I_L) + \\ & c_2((1 - \alpha)\beta TV_I + \gamma I_L - (\mu + \omega)I_A - \sigma I_A Z) + \\ & c_3(\omega N I_A - \mu_v V_I) + \left(1 - \frac{Z_0}{Z}\right) (\pi_1 + \beta_1 I_A - \mu_1 Z). \end{aligned} \quad (3.53)$$

From (3.53) we extract coefficients of all linear terms associated with the infectious classes in equation form and equate them to zero to solve for, c_1 , c_2 and c_3 . Thus,

$$c_2 \gamma - (\mu + \gamma)c_1 = 0, \quad (3.54)$$

$$\beta_1 + c_3 \omega N - c_2(\mu + \omega) = 0, \quad (3.55)$$

$$\beta T_0 - c_3 \mu_v = 0. \quad (3.56)$$

Solving equations (3.54) - (3.56) gives

$$\begin{aligned} c_1 &= \frac{\gamma(\mu_v \beta_1 + \omega N \beta T_0)}{\mu_v(\mu + \gamma)(\mu + \omega)}, \\ c_2 &= \frac{\mu_v \beta_1 + \omega N \beta T_0}{\mu_v(\mu + \omega)}, \\ c_3 &= \frac{\beta T_0}{\mu_v}. \end{aligned}$$

If we now substitute $\pi = \mu T_0$, $\pi_1 = \mu Z_0$, and compactly rewrite (3.53) in

terms of c_2 , we obtain

$$\begin{aligned}
 \dot{U} &= -\frac{\mu}{T}(T - T_0)^2 - \beta TV_I - \left(\frac{\mu}{\mu + \gamma}\right) c_2 \alpha \beta TV_I - c_2 \sigma I_A Z + \\
 &\quad c_2 \beta TV - \frac{\mu_1}{Z}(Z - Z_0)^2 - \beta_1 Z_0 \frac{I_A}{Z} \\
 &= -\frac{\mu}{T}(T - T_0)^2 - \frac{\mu_1}{Z}(Z - Z_0)^2 + \\
 &\quad \left(\frac{(1 - \alpha)\mu + \gamma}{\mu + \gamma} c_2 - 1\right) \beta TV_I - c_2 \sigma I_A Z - \beta_1 Z_0 \frac{I_A}{Z}.
 \end{aligned} \tag{3.57}$$

To find the condition that guarantees (3.57) to be negative definite, we consider the coefficient of the term βTV_I given by

$$c_4 = \left(\frac{(1 - \alpha)\mu + \gamma}{\mu + \gamma} c_2 - 1\right).$$

If we substitute c_2 in the above expression we get

$$c_4 = \frac{[(1 - \alpha)\mu + \gamma]\omega N \beta T_0}{\mu_v(\mu + \gamma)(\mu + \omega)} + \frac{\beta_1[(1 - \alpha)\mu + \gamma]}{(\mu + \omega)(\mu + \gamma)}. \tag{3.58}$$

If we let $c_5 = \frac{\mu + \omega + \sigma Z_0}{\mu + \omega} \left(1 + \frac{\beta_1}{\omega N \beta T_0}\right)$, then (3.58) can be written as follows

$$c_4 = c_5 R_0.$$

Since $c_5 > 1$, and we require that $c_4 - 1 < 0$, then $c_4 - 1 = c_5 R_0 - 1 < 1$ implies $R_0 < 1/c_5 < 1$. This completes the proof of Theorem 3.5.2. \square

3.5.3 Stability analysis of endemic equilibrium

Since we now know that the system of equations (3.1)-(3.5) has a unique endemic equilibrium when $R_0 > 1$, then, to study the stability of the endemic equilibrium we use the center manifold theory. We begin by renaming the

variables, i.e., Let $T = x_1$, $I_L = x_2$, $I_A = x_3$, $V_I = x_4$, $Z = x_5$. We also let β be the bifurcation parameter and $\frac{dx_l}{dt} = f_l$, for $l = 1, 2, 3, 4, 5$. Thus, equations (3.1)-(3.5) can be written as follows:

$$\dot{x}_1 = \pi - \mu x_1 - \beta x_1 x_4, \quad (3.59)$$

$$\dot{x}_2 = \alpha \beta x_1 x_4 - (\mu + \gamma) x_2, \quad (3.60)$$

$$\dot{x}_3 = (1 - \alpha) \beta x_1 x_4 + \gamma x_2 - (\mu + \omega) x_3 - \sigma x_3 x_5, \quad (3.61)$$

$$\dot{x}_4 = \omega N x_3 - \mu_v x_4, \quad (3.62)$$

$$\dot{x}_5 = \pi_1 + \beta_1 x_3 - \mu_1 x_5, \quad (3.63)$$

with $R_0 = 1$ corresponding to $\beta = \beta^* = \frac{\mu_v(\mu + \gamma)(\mu + \omega + \sigma Z_0)}{\omega N T_0 [\alpha \gamma + (\mu + \gamma)(1 - \alpha)]}$.

Theorem 3.5.3. *The endemic equilibrium is locally asymptotically stable for $R_0 > 1$ but close to one.*

Proof. The linearization matrix of the system of equations (3.59)-(3.63) at a DFE when $\beta = \beta^*$ is given by

$$J(E_0, \beta^*) = \begin{pmatrix} -\mu & 0 & 0 & -\beta^* T_0 & 0 \\ 0 & -\mu - \gamma & 0 & \alpha \beta^* T_0 & 0 \\ 0 & \gamma & -\mu - \omega - \sigma Z_0 & (1 - \alpha) \beta^* T_0 & 0 \\ 0 & 0 & \omega N & -\mu_v & 0 \\ 0 & 0 & \beta_1 & 0 & -\mu_1 \end{pmatrix}. \quad (3.64)$$

The eigenvalue values obtained from solving a characteristic equation are

$$\begin{aligned} \lambda_{11} &= 0, \quad \lambda_{12} = -\mu, \quad \lambda_{13} = -\mu_1, \\ \lambda_{14,15} &= -\frac{1}{2}(c_{11} + c_{12} + c_{13}) \pm \frac{1}{2}\sqrt{(c_{11} - c_{12} - c_{13})^2 + 4c_{14}}, \end{aligned} \quad (3.65)$$

where, $c_{11} = \mu + \gamma$, $c_{12} = \mu + \omega + \sigma Z_0$, $c_{13} = \mu_v$, and $c_{14} = \omega N(1 - \alpha)\beta^* T_0$. Noting that $\lambda_{12,13,14,15} < 0$ and $\lambda_{11} = 0$ we can now apply the center manifold theory to prove the local stability of the endemic equilibrium. The left eigenvectors associated to the zero eigenvalue of $J(E_0, \beta^*)$ are obtained by solving the equation

$$\mathbf{v}[J(E_0, \beta^*)] = 0, \quad (3.66)$$

for $\mathbf{v} = (v_1, v_2, v_3, v_4, v_5)$ which gives

$$\begin{aligned} v_1 = 0, \quad v_2 = \frac{\gamma\omega N}{(\mu + \gamma)(\mu + \omega + \sigma Z_0)}v_4, \quad v_3 = \frac{\omega N}{\mu + \omega + \sigma Z_0}v_4, \\ v_4 = v_4 > 0, \quad \text{and } v_5 = 0. \end{aligned} \quad (3.67)$$

We can clearly see that $v_2 > 0$ and $v_3 > 0$. The right eigenvectors associated to the zero eigenvalue of $J(E_0, \beta^*)$ are obtained by solving the equation

$$[J(E_0, \beta^*)]\mathbf{w}^t = 0, \quad (3.68)$$

for $\mathbf{w} = (w_1, w_2, w_3, w_4, w_5)$ which gives

$$\begin{aligned} w_1 = -\frac{\omega N\beta^* T_0}{\mu\mu_v}w_3, \quad w_2 = \frac{\alpha\beta^* T_0}{\gamma\mu}w_4, \quad w_3 = w_3 > 0 \\ w_4 = \frac{\omega N}{\mu_v}w_3, \quad w_5 = \frac{\beta_1}{\mu_1}w_3, \end{aligned} \quad (3.69)$$

from which it is clear that, $w_1 < 0$, $w_2 > 0$, $w_4 > 0$ and $w_5 > 0$. Next we compute the values of a and b in Theorem 2.4.2. Since, $v_1 = v_5 = 0$ and we have no non-linear term(s) in equation (3.62), we will only compute the partial derivative of f_2 and f_3 . The associated partial derivative with the

system of equations (3.59)-(3.63) are as follows:

$$\begin{aligned}\frac{\partial^2 f_2}{\partial x_1 \partial x_4} &= \frac{\partial^2 f_2}{\partial x_4 \partial x_4} = \alpha \beta^*, \\ \frac{\partial^2 f_3}{\partial x_1 \partial x_4} &= \frac{\partial^2 f_3}{\partial x_4 \partial x_4} = (1 - \alpha) \beta^*, \\ \frac{\partial^2 f_3}{\partial x_3 \partial x_5} &= \frac{\partial^2 f_3}{\partial x_5 \partial x_3} = -\sigma.\end{aligned}$$

It follows that

$$\begin{aligned}a &= 2v_2 w_1 w_4 \frac{\partial^2 f_2}{\partial x_1 \partial x_4} + 2v_3 w_1 w_4 \frac{\partial^2 f_3}{\partial x_1 \partial x_4} + 2v_3 w_3 w_5 \frac{\partial^2 f_3}{\partial x_3 \partial x_5} \\ &= -2\omega w_3^2 N \left(\frac{\beta^*}{\mu \mu_v} + \frac{\beta_1}{\mu_1(\mu + \omega + \sigma Z_0)} \right) < 0.\end{aligned}\tag{3.70}$$

Now, for b the only terms that does not vanish are

$$\begin{aligned}\frac{\partial^2 f_2}{\partial x_1 \partial \beta^*} &= \alpha T_0, \\ \frac{\partial^2 f_3}{\partial x_1 \partial \beta^*} &= (1 - \alpha) T_0.\end{aligned}$$

Hence,

$$\begin{aligned}b &= v_2 w_4 \frac{\partial^2 f_2}{\partial x_1 \partial \beta^*} + v_3 w_4 \frac{\partial^2 f_3}{\partial x_1 \partial \beta^*} \\ &= \frac{\omega N}{\mu_v \beta} w_3 > 0.\end{aligned}\tag{3.71}$$

Therefore, $a < 0$, $b > 0$ and there exist a supercritical bifurcation at $R_0 = 1$ which means E_0 loses stability and E_{11} as the only equilibrium that exists when $R_0 > 1$, becomes stable but closer to 1. \square

3.6 Summary

Through the analysis of the behavior of the model we showed that the constant virus production model was well posed. Hence, the model was used to

study the dynamics of HIV-1. We calculated reproduction number, which played a vital role in the analysis of the disease free and endemic equilibrium points. We obtained a unique disease free equilibrium point and when $R_0 > 1$ we obtained a unique endemic equilibrium point. The disease-free equilibrium point was globally stable when $R_0 < 1$ and the endemic equilibrium point was locally asymptotically stable for $R_0 > 1$ but close to 1. We shall in the following chapter modify this model to incorporate the effects of Tat and SSu72 and use numerical multi-domain spectral methods to analyze the model.

Chapter 4

Analysing HIV-1 model incorporating Tat and Ssu72 proteins

4.1 Introduction

In this chapter we formulate a model incorporating Tat and Ssu72. The constant virus production model from chapter 3 is modified to incorporate the extra equations that will capture the dynamics of Tat and Ssu72. We also discuss the multistage spectral relaxation method and use it to analyze the HIV-1 model incorporating Tat and Ssu72. In the analysis we look at the influence of Tat and Ssu72 on the HIV-1 dynamics, i.e., activation of latently infected $CD4^+$ T cells and the response of $CD8^+$ T cells.

4.2 Model formulation

Recently it has been discovered that, it is not only the T-cells that drives the dynamics of HIV-1 but also the existence of the protein called Tat. According to the Salk team [18], HIV-1 cannot live without the existence of Tat. The Tat protein serves as a HIV-1 scout for suitable environment for the virus to replicate [18]. When the environment has been discovered, only then it kicks off the HIV's transcription to enable the virus to replicate and spread [18]. The Salk team were able to ascertain that Tat has a mutualistic partner, Ssu72. Ssu72 plays a key role in activation process of HIV infection replication, by binding directly to Tat and also builds a feedback loop to speed up the process [18].

HIV transcription is regulated by the HIV associated Tat. Tat is a transactivator protein that contributes to the transactivation of viral and cellular genes [26]. Tat protein is produced after the small number of RNA transcriptions of HIV-1 are produced [36]. Tat enhances the transcription of the HIV dsDNA [35, 36], by binding to the small RNA cellular factors and mediating the phosphorylation which result in increasing transcription of all HIV genes [36]. Not only in infection production does the cellular transcription regulate HIV LTR driven expression, but also act as a switch to latently infected cell [36]. These cells serve as a reservoir of infected cells, that prevents the clearing or eradication of the virus.

The rate of change of the two proteins (Tat and Ssu72) resemble the dynamics of mutualism. This is due to the fact that each proteins influences the growth

of the other. We assume the growth of each protein to be saturated. The dynamics can be compactly represent as

$$\frac{dT_a}{dt} = r_1 T_a \left(1 - \frac{T_a}{K_{tat}} + b_1 \frac{S_u}{K_{Ssu}} \right), \quad (4.1)$$

$$\frac{dS_u}{dt} = r_2 S_u \left(1 - \frac{S_u}{K_{Ssu}} + b_2 \frac{T_a}{K_{tat}} \right). \quad (4.2)$$

r_1 and r_2 are constant recruitment rates of proteins Tat and Ssu72, respectively. K_{tat} and K_{Ssu} are the carrying capacities of proteins Tat and Ssu72, respectively. The mutual effects of Tat on Ssu72 and of Ssu72 on Tat are described by b_2 and b_1 , respectively.

The population of latently infected cells require activation process for them to be in an actively infectious stage. This is the stage where Tat and Ssu72 play a huge role. These proteins are the bridge from latently infected stage to actively infectious stage thereby speeding up the activation process.

Incorporating equations (4.1) and (4.2) in the first model will result with the following systems of equations;

$$\frac{dT}{dt} = \pi - \mu T - \beta TV_I, \quad (4.3)$$

$$\frac{dI_L}{dt} = \alpha \beta TV_I - (\mu + \gamma + \gamma(T_a, S_u))I_L, \quad (4.4)$$

$$\frac{dI_A}{dt} = (1 - \alpha)\beta TV + (\gamma + \gamma(T_a, S_u))I_L - (\mu + \omega + \omega(T_a))I_A - (\sigma + \sigma(T_a))I_A Z, \quad (4.5)$$

$$\frac{dV_I}{dt} = (\omega + \omega(T_a))NI_A - \mu_v V_I, \quad (4.6)$$

$$\frac{dZ}{dt} = \pi_1 + \beta_1 I_A - \mu_1 Z, \quad (4.7)$$

$$\frac{dT_a}{dt} = r_1 T_a \left(1 - \frac{T_a}{K_{tat}} + b_1 \frac{S_u}{K_{Ssu}} \right), \quad (4.8)$$

$$\frac{dS_u}{dt} = r_2 S_u \left(1 - \frac{S_u}{K_{Ssu}} + b_2 \frac{T_a}{K_{tat}} \right), \quad (4.9)$$

where

$$\gamma(T_a, S_u) = \frac{\phi T_a S_u}{(1 + K_{tat})(1 + K_{tat} K_{Ssu})} \text{ is the activation function for}$$

latently infected cells to actively infectious cells.

$$\sigma(T_a) = \frac{\phi_3 T_a}{1 + K_{tat}} \text{ is the lysis function for viral producing cells due to}$$

influence of Tat.

$$\omega(T_a) = \frac{\phi_4 T_a}{1 + K_{tat}} \text{ is the killing rate function due to influence of Tat.}$$

The functions (γ, σ, ω) above capture the effects of Tat and Ssu72 on the HIV-1 dynamics, where ϕ is the activation rate of latently infected cells by Tat and Ssu72, ϕ_3 is the lysis rate due to the effects of Tat and ϕ_4 is the killing rate of infected $CD4^+$ T cells due to the influence of Tat. These functions were selected in such a way that the assumption of saturation effects of the two proteins is met.

4.3 Analysis of Tat and Ssu72 model

In this section we analyse the behavior of Tat and Ssu72, through studying the equilibrium points and their stability with respect to equations (4.1) and (4.2).

4.3.1 Equilibrium points for Tat and Ssu72 dynamics model

Consider (4.1) and (4.2). This system of two equations have 4 equilibrium points given by

$$(0, 0), (0, K_{Ssu}), (K_{tat}, 0) \text{ and } (T_a^*, S_u^*), \quad (4.10)$$

where $T_a^* = \frac{1+b_1}{1-b_1b_2}K_{tat}$ and $S_u^* = \frac{1+b_2}{1-b_1b_2}K_{Ssu}$. The equilibrium point (T_a^*, S_u^*) is biological meaningful if $b_1b_2 < 1$.

4.3.2 Stability analysis of equilibria of Tat and Ssu72 dynamics

In this subsection we study the stability of the equilibria given by equation (4.10)

$$E_{00}^* = (0, 0). \quad (4.11)$$

The Jacobian matrix of the system at the origin is given by

$$J(E_{00}^*) = \begin{bmatrix} r_1 & 0 \\ 0 & r_2 \end{bmatrix}. \quad (4.12)$$

Since the Jacobian matrix is a diagonal matrix we can easily deduce that the two eigenvalues are given by

$$\lambda_{01} = r_1, \lambda_{02} = r_2. \quad (4.13)$$

Since $r_1 > 0$ and $r_2 > 0$, we therefore conclude that the origin is an unstable node.

Now consider the equilibrium point,

$$E_{11}^* = \left(\frac{1+b_1}{1-b_1b_2} K_{tat}, \frac{1+b_2}{1-b_1b_2} K_{Ssu} \right). \quad (4.14)$$

The Jacobian matrix of the endemic equilibrium is give by

$$J(E_{11}^*) = \begin{bmatrix} -\frac{r_1(1+b_1)}{1-b_1b_2} & \frac{r_1b_1(1+b_1)K_{tat}}{(1-b_1b_2)K_{Ssu}} \\ \frac{r_2b_2(1+b_2)K_{Ssu}}{(1-b_1b_2)K_{tat}} & -\frac{r_2(1+b_2)}{1-b_1b_2} \end{bmatrix}. \quad (4.15)$$

To conclude on the stability of (4.14), we have to show that the following conditions,

1. $tr(J(E_{11}^*)) < 0$,
2. $det(J(E_{11}^*)) > 0$,

hold for

$$\lambda^2 - tr(J(E_{11}^*))\lambda + det(J(E_{11}^*)) = 0, \quad (4.16)$$

such that its solutions are negative. Now the

$$tr(J(E_{11}^*)) = - \left[\frac{r_1(1+b_1) + r_2(1+b_2)}{1-b_1b_2} \right] < 0, \text{ provided } b_1b_2 < 1. \quad (4.17)$$

$$\det(J(E_{01}^*)) = \frac{r_1 r_2 (1 + b_1)(1 + b_2)}{1 - b_1 b_2} > 0, \text{ provided } b_1 b_2 < 1. \quad (4.18)$$

Hence, E_{11}^* is a stable node provided $b_1 b_2 < 1$.

Finally, we show that the other equilibria are saddle nodes. The Jacobian matrices at the two equilibria are given by

$$J(0, K_{Ssu}) = \begin{bmatrix} r_1(1 - b_1) & 0 \\ r_2 \frac{K_{Ssu}}{K_{tat}} & -r_2 \end{bmatrix}, \quad (4.19)$$

$$J(K_{tat}, 0) = \begin{bmatrix} -r_1 & r_1 \frac{K_{tat}}{K_{Ssu}} \\ 0 & r_2(1 - b_2) \end{bmatrix}. \quad (4.20)$$

Since the eigenvalue of (4.19) and (4.20) are real and opposite signs for $b_1 < 1$ and $b_2 < 1$, we conclude that the equilibrium points for each case $((0, K_{Ssu})$ and $(K_{tat}, 0)$), are saddle nodes. Otherwise when $b_1 > 1$ and $b_2 > 1$, both equilibrium points are stable nodes.

4.4 summary

In this chapter we presented an HIV-1 model incorporating Tat and Ssu72. We analysed the mutualistic model, where we obtained the stability region for the four equilibrium point obtained. We were able to show that $(0, 0)$ is a stable node, $(0, K_{Ssu})$ and $(K_{tat}, 0)$ are saddle nodes when $b_1 < 1$ and $b_2 < 1$, respectively. However, we also obtained that $(0, K_{Ssu})$ and $(K_{tat}, 0)$ are also stable nodes when $b_1 > 1$ and $b_2 > 1$, respectively. We also showed that

(T_a^*, S_u^*) is a stable node when $b_1 b_2 < 1$. In the next chapter we discuss the numerical method to be used to analyze the developed model in this chapter.

Chapter 5

Multistage spectral relaxation method algorithm

5.1 Introduction

In this chapter we discuss the recent multistage spectral relaxation method [40], that is used to solve the system of first order differential equations of initial value problems. Most of the problems of such nature in mathematical biology cannot be solved analytically, therefore numerical methods have to be adopted. Various numerical methods to solve such type of problems have been developed, including, Euler's method, MatLab built in solvers (ode45, ode113, ode23), Runge Kutta method and multi-step methods. Some of these methods have been reported to be disadvantageous for their accuracy, efficiency, convergence and more over their performance on large interval of integration [41].

A vast number of research has been conducted to modify the existing and/or to develop new methods. Most of these methods have been extended, through redefining (sub-dividing large interval) the interval of integration by constructing multistage methods. The few examples of such methods are; multistage-homotopy perturbation method [43, 44], multistage variational iteration method [45], multistage Adomain decomposition method [46], multistage-differential transform method [47, 48]. However, the use of these methods is computationally tedious, since the methods seek analytical solutions and they also suffer from certain limitations such as small convergence [41]. For chaotic systems some of these methods fail to analytically solve the system [41].

The recent methods that Dlamini et. al. [40] and Motsa et. al. [41], developed are namely, multistage spectral relaxation method (MSRM), piecewise-successive linearisation method (PSLM), respectively. These methods have been shown to solve chaotic systems, e.g., Lorenz, Genesio-Tesi, Rossler, Chen, Liu, Arneodo-Coullet and the Rikitake system [40, 41, 42]. The MSRM has been shown to be preferred over PSLM [40]. The computational time of MSRM against that of PSLM and the decoupling on MSRM against the linearisation on PSLM of the original equations, makes the MSRM efficient to use and rely on. The MSRM being further compared to MatLab built in solvers, was shown to be accurate, efficient and reliable [40]. Thus, in this paper we use MSRM to solve the developed system, which shall be validated using MatLab built in solvers.

5.2 Multistage spectral relaxation method

The method to be used to analyze the Model incorporating Tat and Ssu72 is known as multistage spectral relaxation method (MSRM) [40, 42]. The MSRM is a multistage iterative scheme which is based on blending a Gauss-Siedel method and spectral collocation integration to decouple and solve, respectively the system of first order differential equations of initial value problems. The first derivatives are approximated using the Chebychev spectral method at each collocation point. For accuracy, the interval is then subdivided into small intervals such that the final value on each interval is the initial value of the succeeding interval. The nonlinear first order differential equations to be solved are of the form

$$\begin{aligned} \dot{x}_r(t) + \sum_{k=1}^m \alpha_{r,k} x_k(t) + f_r[x_1(t), \dots, x_m(t)] &= g_r, \\ x_r(0) &= x_r^*, \quad r = 1, 2, \dots, m, \end{aligned} \quad (5.1)$$

where x_r are the unknown variables and x_r^* are the corresponding initial conditions, $\alpha_{r,k}$ and g_r are known constant input parameters and f_r is the nonlinear component of the r th equation, and the dot denotes differentiation with respect to time t .

The interval of integration is given by $t \in [0, t_F]$ from which (5.1) is solved. This interval is therefore decomposed to sub-interval, $\Phi_i = [t_{i-1}, t_i]$, where

$i = 1, 2, 3, \dots, F$. Therefore, on the first interval, we solve

$$\begin{aligned} \dot{x}_r^1(t) + \sum_{k=1}^m \alpha_{r,k} x_k^1(t) + f_r[x_1^1(t), x_2^1(t), \dots, x_m^1(t)] &= g_r, \\ x_r^1(t_0) &= x_{r0}^*, \end{aligned} \quad (5.2)$$

where $r = 1, 2, \dots, m$.

On the subsequent intervals $\Phi_i = [t_{i-1}, t_i]$ for $i \geq 2$, we solve

$$\begin{aligned} \dot{x}_r^i(t) + \sum_{k=1}^m \alpha_{r,k} x_k^i(t) + f_r[x_1^i(t), x_2^i(t), \dots, x_m^i(t)] &= g_r, \\ x_r^i(t_{i-1}) &= x_r^{i-1}(t_{i-1}), \end{aligned} \quad (5.3)$$

where $r = 1, 2, \dots, m$ and $i = 2, 3, \dots, F$. It may be noted that F denote the number of intervals to which the solution is to be computed into. From these sub-intervals, we evaluate the solution to the problem using the pseudo-spectral collocation method. One may note that the equations are treated as decoupled system, i.e., a Gauss Siedel Method is used.

5.3 Algorithm

Here, we illustrate the algorithm for the problem (5.3). Equation (5.3) can be rewritten as a system of equations as follows

$$\dot{x}_r^i(t) + \alpha_{r,r} x_r^i(t) = g_r - \sum_{k=1}^m (1 - \delta_{r,k}) \alpha_{r,k} x_k^i(t) - f_r[x_1^i(t), x_2^i(t), \dots, x_m^i(t)], \quad (5.4)$$

$$x_r^i(t_{i-1}) = x_r^{i-1}(t_{i-1}),$$

where $r = 1, 2, \dots, m$, $i = 1, 2, \dots, F$ and $\delta_{r,k}$ is a Kronecker delta function such that

$$\delta_{r,k} = \begin{cases} 1, & k = r, \\ 0, & k \neq r. \end{cases} \quad (5.5)$$

If we let $\hat{f}_r = g_r - \sum_{k=1}^m (1 - \delta_{r,k}) \alpha_{r,k} x_k^i(t) - f_r[x_1^i(t), x_2^i(t), \dots, x_m^i(t)]$, equation (5.4) can be compactly written as

$$\begin{aligned} \dot{x}_r^i(t) + \alpha_{r,r} x_r^i(t) &= \hat{f}_r[g_r, x_1^i(t), x_2^i(t), \dots, x_m^i(t)], \\ x_r^i(t_{i-1}) &= x_r^{i-1}(t_{i-1}), \end{aligned} \quad (5.6)$$

where $r = 1, 2, \dots, m$ and $i = 1, 2, \dots, F$. Now, that we have achieved our results we then solve (5.6) in the first interval, i.e., $i = 1$

$$\dot{x}_{1,s+1}^1(t) + \alpha_{1,1} x_{1,s+1}^1(t) = \hat{f}_1[g_1, x_{1,s}^1(t), x_{2,s}^1(t), \dots, x_{m,s}^1(t)], \quad (5.7)$$

$$\dot{x}_{2,s+1}^1(t) + \alpha_{2,2} x_{2,s+1}^1(t) = \hat{f}_2[g_2, x_{1,s+1}^1(t), x_{2,s}^1(t), \dots, x_{m,s}^1(t)], \quad (5.8)$$

\vdots

$$\dot{x}_{m,s+1}^1(t) + \alpha_{m,m} x_{m,s+1}^1(t) = \hat{f}_m[g_m, x_{1,s+1}^1(t), \dots, x_{m-1,s+1}^1(t), x_{m,s}^1(t)], \quad (5.9)$$

subject to

$$x_1^1(t_0) = x_{r0}^*. \quad (5.10)$$

The derivatives of the unknown variables are approximated by

$$\frac{dx_{r,s+1}^1}{dt}(t_j) = \sum_{k=0}^M \mathbf{D}_{jk} x_{r,s+1}^1(\tau_k) = \mathbf{D} \mathbf{X}_{r,s+1}^1, \quad (5.11)$$

$$j = 0, 1, 2, \dots, M$$

where $\mathbf{D} = \frac{2}{t_1 - t_0} D$ and $\mathbf{X}_{r,s+1}^1 = [x_{r,s+1}^1(\tau_0), x_{r,s+1}^1(\tau_1), \dots, x_{r,s+1}^1(\tau_N)]$ are the vectors function at the collocation points τ_j , with

$$\tau_j = \cos\left(\frac{\pi j}{N}\right), \quad j = 0, 1, \dots, M \quad (5.12)$$

being defined as Chebyshev-Gauss-Lobatto collocation points, where the extrema of the M th order Chebyshev polynomial are given by

$$T_M(\tau) = \cos(M \cos^{-1} \tau). \quad (5.13)$$

The linear transformation of the interval $[t_{i-1}, t_i]$ to the interval $[-1, 1]$ in which the spectral method is defined is given by

$$t = \frac{(t_i - t_{i-1})}{2} \tau + \frac{(t_i + t_{i-1})}{2}, i = 1, 2, \dots, F. \quad (5.14)$$

After applying the Chebyshev spectral collocation method on (5.3), we obtain the following result

$$\begin{aligned} \mathbf{A}_r \mathbf{X}_{r,s+1}^1 &= \mathbf{B}_r^1, \\ \mathbf{X}_r^1(\tau_0) &= \mathbf{X}_r^*(\tau_0), \end{aligned} \quad (5.15)$$

where \mathbf{A}_r and \mathbf{B}_r^1 are known term. Thus, we solve for $\mathbf{X}_{r,s+1}^1$ subject to the given initial conditions. For the intervals $i = 2, 3, \dots, F$ we solve the same problem (5.6),

$$\begin{aligned} \mathbf{A}_r \mathbf{X}_{r,s+1}^i &= \mathbf{B}_r^i, \\ \mathbf{X}_r^i(\tau_0) &= \mathbf{X}_r^{i-1}(\tau_M), \end{aligned} \quad (5.16)$$

where

$$\mathbf{A} = \begin{bmatrix} \mathbf{D} + \alpha_{1,1} \mathbf{I} \\ \mathbf{D} + \alpha_{2,2} \mathbf{I} \\ \vdots \\ \mathbf{D} + \alpha_{m,m} \mathbf{I} \end{bmatrix}, \quad \mathbf{B}^i = \begin{bmatrix} \hat{f}_1 \\ \hat{f}_2 \\ \vdots \\ \hat{f}_m \end{bmatrix}, \quad (5.17)$$

$$\mathbf{X}_{r,s+1}^i = [x_{1,s+1}, x_{2,s+1}, \dots, x_{7,s+1}]^T \quad (5.18)$$

with $r = 1, 2, \dots, m$ and \mathbf{I} is an Identity matrix.

5.3.1 Application of the MSRM on the model incorporating Tat and Ssu72

Consider the following model

$$\begin{aligned}
\dot{T} &= \pi - \mu T - \beta TV_I, \\
\dot{I}_L &= \alpha \beta TV_I - (\mu + \gamma + \gamma(T_a, S_u)) I_L, \\
\dot{I}_A &= (1 - \alpha) \beta TV + (\gamma + \gamma(T_a, S_u)) I_L - (\mu + \omega + \omega(T_a)) I_A - (\sigma + \sigma(T_a)) I_A Z, \\
\dot{V}_I &= (\omega + \omega(T_a)) N I_A - \mu_v V_I, \\
\dot{Z} &= \pi_1 + \beta_1 I_A - \mu_1 Z, \\
\dot{T}_a &= r_1 T_a \left(1 - \frac{T_a}{K_{tat}} + b_1 \frac{S_u}{K_{Ssu}} \right), \\
\dot{S}_u &= r_2 S_u \left(1 - \frac{S_u}{K_{Ssu}} + b_2 \frac{T_a}{K_{tat}} \right),
\end{aligned} \tag{5.19}$$

with positive parameters and the functions $\gamma(T_a, S_u)$, $\sigma(T_a)$, $\omega(T_a)$ defined as saturating functions. The dot define the derivative with respect to time.

To solve (5.19), let

$$x_1 = T, \ x_2 = I_L, \ x_3 = I_A, \ x_4 = V_I, \ x_5 = Z, \ x_6 = T_a, \ x_7 = S_u, \tag{5.20}$$

such that (5.19) is rewritten in following form

$$\dot{x}_1 = \pi - \mu x_1 - \beta x_1 x_4, \quad (5.21)$$

$$\dot{x}_2 = \alpha \beta x_1 x_4 - (\mu + \gamma + \gamma(x_6, x_7)) x_2, \quad (5.22)$$

$$\dot{x}_3 = (1 - \alpha) \beta x_1 x_4 + (\gamma + \gamma(x_6, x_7)) x_2 - (\mu + \omega + \omega(x_6)) x_2 - (\sigma + \sigma(x_6)) x_3 x_5, \quad (5.23)$$

$$\dot{x}_4 = (\omega + \omega(x_6)) N x_3 - \mu_v x_4, \quad (5.24)$$

$$\dot{x}_5 = \pi_1 + \beta_1 x_3 - \mu_1 x_5, \quad (5.25)$$

$$\dot{x}_6 = r_1 x_6 \left(1 - \frac{x_6}{K_{tat}} + b_1 \frac{x_7}{K_{Ssu}} \right), \quad (5.26)$$

$$\dot{x}_7 = r_2 x_7 \left(1 - \frac{x_7}{K_{Ssu}} + b_2 \frac{x_6}{K_{tat}} \right), \quad (5.27)$$

subject to

$$x_1(0) > 0, \ x_2(0) \geq 0, \ x_3(0) \geq 0, \ x_4(0) \geq 0, \ x_5(0) > 0, \ x_6(0) \geq 0, \ x_7(0) \geq 0. \quad (5.28)$$

Now if we apply the Gauss Siedel method we obtain

$$\dot{x}_{1,s+1} + \mu x_{1,s+1} + \beta x_{4,s} x_{1,s+1} = \pi, \quad (5.29)$$

$$\dot{x}_{2,s+1} + (\mu + \gamma + \gamma(x_{6,s}, x_{7,s}))x_{2,s+1} = \alpha \beta x_{4,s} x_{1,s+1}, \quad (5.30)$$

$$\begin{aligned} \dot{x}_{3,s+1} + (\mu + \omega + \omega(x_6) + (\sigma + \sigma(x_6))x_{5,s})x_{3,s+1} &= (1 - \alpha)\beta x_{4,s} x_{1,s+1} \\ &+ (\gamma + \gamma(x_{6,s}, x_{7,s}))x_{2,s+1}, \end{aligned} \quad (5.31)$$

$$\dot{x}_{4,s+1} + \mu_v x_{4,s+1} = (\omega + \omega(x_{6,s}))N x_{3,s+1}, \quad (5.32)$$

$$\dot{x}_{5,s+1} + \mu_1 x_{5,s+1} = \pi_1 + \beta_1 x_{3,s+1}, \quad (5.33)$$

$$\dot{x}_{6,s+1} - r_1 x_{6,s+1} - r_1 b_1 \frac{x_{7,s}}{K_{tat}} x_{6,s+1} = r_1 \frac{x_{6,s}^2}{K_{tat}}, \quad (5.34)$$

$$\dot{x}_{7,s+1} - r_2 x_{7,s+1} - r_2 b_2 \frac{x_{6,s+1}}{K_{Ssu}} x_{7,s+1} = r_2 \frac{x_{7,s}^2}{K_{Ssu}}, \quad (5.35)$$

where,

$$\gamma(x_{6,s}, x_{7,s}) = \frac{\phi x_{6,s} x_{7,s}}{(1 + K_{tat})(1 + K_{tat} K_{Ssu})}, \quad (5.36)$$

$$\sigma(x_{6,s}) = \frac{\phi_3 x_{6,s}}{1 + K_{tat}}, \quad (5.37)$$

$$\omega(x_{6,s}) = \frac{\phi_4 x_{6,s}}{1 + K_{tat}}. \quad (5.38)$$

After collocating eqns (5.29)-(5.38) at each point, $j = 0, 1, \dots, n$, we get result that can be compactly written as

$$\mathbf{A}_r X_{r,s+1} = \mathbf{B}_r, \text{ where } r = 1, 2, \dots, 7, \quad (5.39)$$

with

$$\mathbf{A} = \begin{bmatrix} \mathbf{D} + \mu\mathbf{I} + \mathbf{diag}(\beta x_{4,s}) \\ \mathbf{D} + (\mu + \gamma)\mathbf{I} + \mathbf{diag}(\gamma(x_{6,s}, x_{7,s})) \\ \mathbf{D} + (\mu + \omega)\mathbf{I} + \mathbf{diag}(\omega(x_{6,s}) + \sigma x_{5,s} + \sigma(x_{6,s})x_{5,s}) \\ \mathbf{D} + \mu_v\mathbf{I} \\ \mathbf{D} + \mu_1\mathbf{I} \\ \mathbf{D} - r_1\mathbf{I} - \mathbf{diag}\left(r_1 b_1 \frac{x_{7,s}}{K_{tat}}\right) \\ \mathbf{D} - r_2\mathbf{I} - \mathbf{diag}\left(r_2 b_2 \frac{x_{6,s+1}}{K_{Ssu}}\right) \end{bmatrix}, \quad (5.40)$$

$$\mathbf{B} = \begin{bmatrix} \pi \\ \alpha\beta x_{4,s}x_{1,s+1} \\ (1 - \alpha)\beta x_{4,s}x_{1,s+1} + (\gamma + \gamma(x_{6,s}, x_{7,s}))x_{2,s+1} \\ (\omega + \omega(x_{6,s}))Nx_{3,s+1} \\ \pi_1 + \beta_1 x_{3,s+1} \\ \frac{x_{6,s}^2}{r_1 K_{tat}} \\ \frac{x_{7,s}^2}{r_2 K_{Ssu}} \end{bmatrix} \quad (5.41)$$

and

$$X_{r,s+1} = [x_{1,s+1}, x_{2,s+1}, \dots, x_{7,s+1}]^T \quad (5.42)$$

Using the algorithm we solve (5.39) on the interval $i = 1, 2, \dots, F$, subject to the initial conditions (5.28).

5.4 Summary

In this chapter, a brief introduction and algorithm on the multistage spectral relaxation method (MSRM) was given. We showed the application of the

MRSM by solving the developed model in this chapter. In the next chapter we use the multistage spectral relaxation method to analyze the developed model.

Chapter 6

Numerical simulations

6.1 Introduction

In this chapter we present the numerical results obtained through solving the algorithm given in section 5.3. Solutions of the model incorporating Tat and Ssu72 are compared against the solutions of the model without them. Conclusion are then taken based on the behavior of solutions of the two models, whether there exist variation between the two model or not. We vary the recruitment rate of $CD8^+$ T cells to test the killing rate of $CD8^+$ T cells subject to Tat and we vary the initial condition of Tat and Ssu72 to test for the effects of proteins on activation of resting virus.

We specifically investigate initial condition of Tat and Ssu72 because from literature we ascertain that Tat and Ssu72 proteins are responsible for activation of latently infected $CD4^+$ T cells and replication of the virus. By varying these aspect, we investigate the role and effect of the two proteins

on progression of the HIV infection. We seek a threshold value of the two proteins required to awake the resting virus on the $CD4^+$ T cells. Provided the threshold is found, then the immune system (cytotoxic killer cells) can eradicate the actively infectious $CD4^+$ T cells and clear the latent reservoirs.

The solutions of the model are obtained using the multistage spectral relaxation method (MSRM). These results are validated using the MatLab built in solvers (ode45). The chosen number of grid points are $M = 10$ and five number of iteration. The interval of integration was chosen to be 300 days, that is, $t \in [0, 300]$, and this interval is divided into 10000 sub-intervals. It may be noted that these chosen constant gave accurate results in comparison with the MatLab built in solver (ode45).

Table 6.1: Estimated values of parameters

Parameters	Estimated Values	Sources
π	20	Fitted
π_1	1 or 10	Fitted
μ	0.02	[17, 39]
μ_1	0.1	Fitted
μ_v	2.4	[17]
β	2.4×10^{-4}	[39]
β_1	0.33	Fitted
α	0.9	Fitted
γ	0.2	Fitted
ω	0.24	[39]
σ	4.5×10^{-4}	Estimated
N	500	[17]
$r_{1,2}$	0.1	Estimated
$b_{1,2}$	0.2	Estimated
$\phi, \phi_{3,4}$	1	Estimated
K_{Ta}, K_{Su}	30	[23]

The initial conditions are given by $T(0) = 1000$, $I_L(0) = 0$, $I_A(0) = 0$ and $V_I(0) = 0.001$. Tat and Ssu72 are chosen to be two-tuples from the values $T_a = [0 \text{ and } 2.0 \times 10^{-6}]$ and $S_u = [0 \text{ and } 2.0 \times 10^{-6}]$ to constitute the four equilibrium points.

6.2 Simulation of results: $\pi_1 = 1$ and $\pi_1 = 10$

Results (in figures) and discussions are presented for each of the cases on which the recruitment rate of CD8⁺ T cells is varied with respect to the initial conditions of Tat and Ssu72.

6.3 Discussion of results: $\pi_1 = 1$ and $\pi_1 = 10$

For each of the four scenarios, we observed that the growth in the virus was associated with the depletion of uninfected CD4⁺ T cells and an increase to infected and infectious compartments. Conversely, decrease in the virus was associated with the increase in uninfected CD4⁺ T cells and a decrease to infected and infectious compartments. In Figures 6.1 and 6.5, after approximately 50 days of duration of infection, the infected and infectious compartments increases rapidly to reach extrema and then decrease exponentially to converge to equilibrium values, while CD4⁺ T cells decreases exponential and converges to an equilibrium values.

In Figure 6.2 and 6.6, we observe that the CD4⁺ T cells temporally decreases but immediately recovers to its initial value, whilst the infected and infectious classes temporally increase but decays to zero. We observed again that, compared to cases 1 and 3, cases 2 and 4 of both scenarios when $\pi_1 = 1$ and $\pi_1 = 10$ yields better results in terms of eradicating the latent reservoirs. What is worth noting is that in cases where Tat is present, latently infected CD4⁺ T cells are activated compared to cases where Ssu72 is present alone.

Case 1: $T_a = 0$ and $S_u = 0$

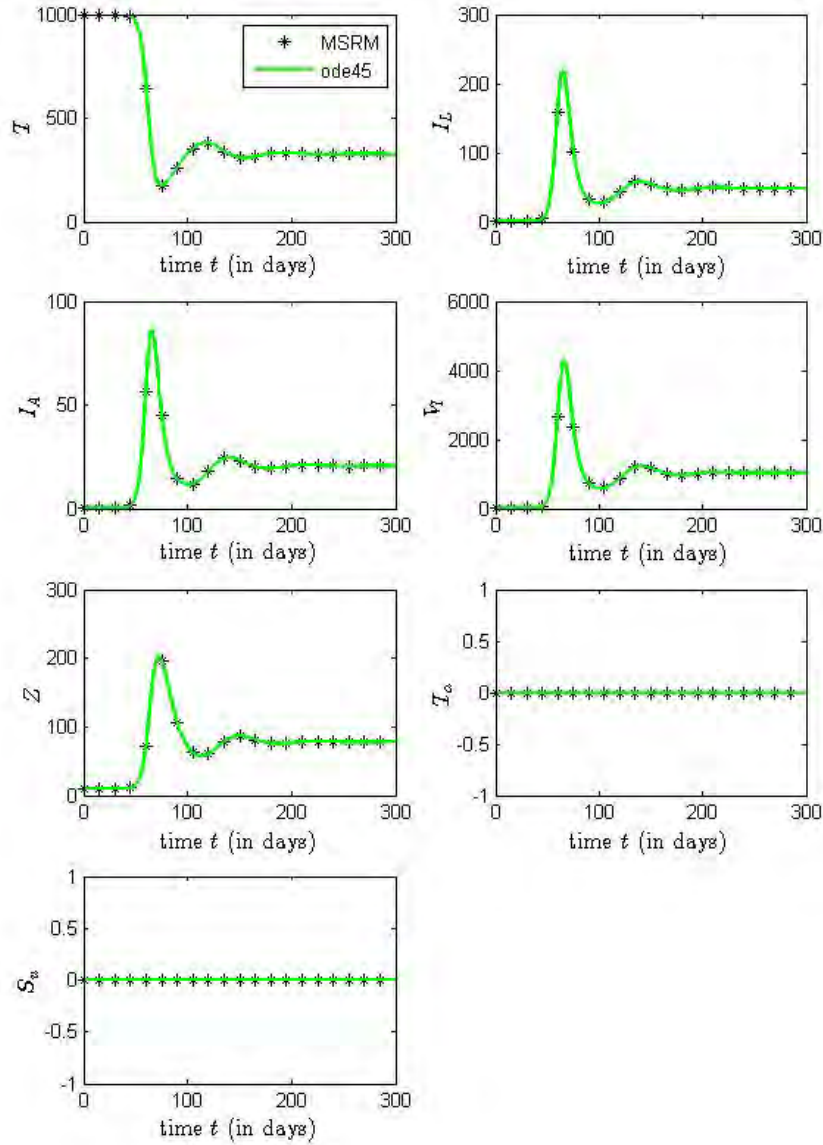


Figure 6.1: Results of the model without Tat and Ssu72, when $\pi_1 = 1$

Case 2: $T_a = 2.0 \times 10^{-6}$ and $S_u = 0$

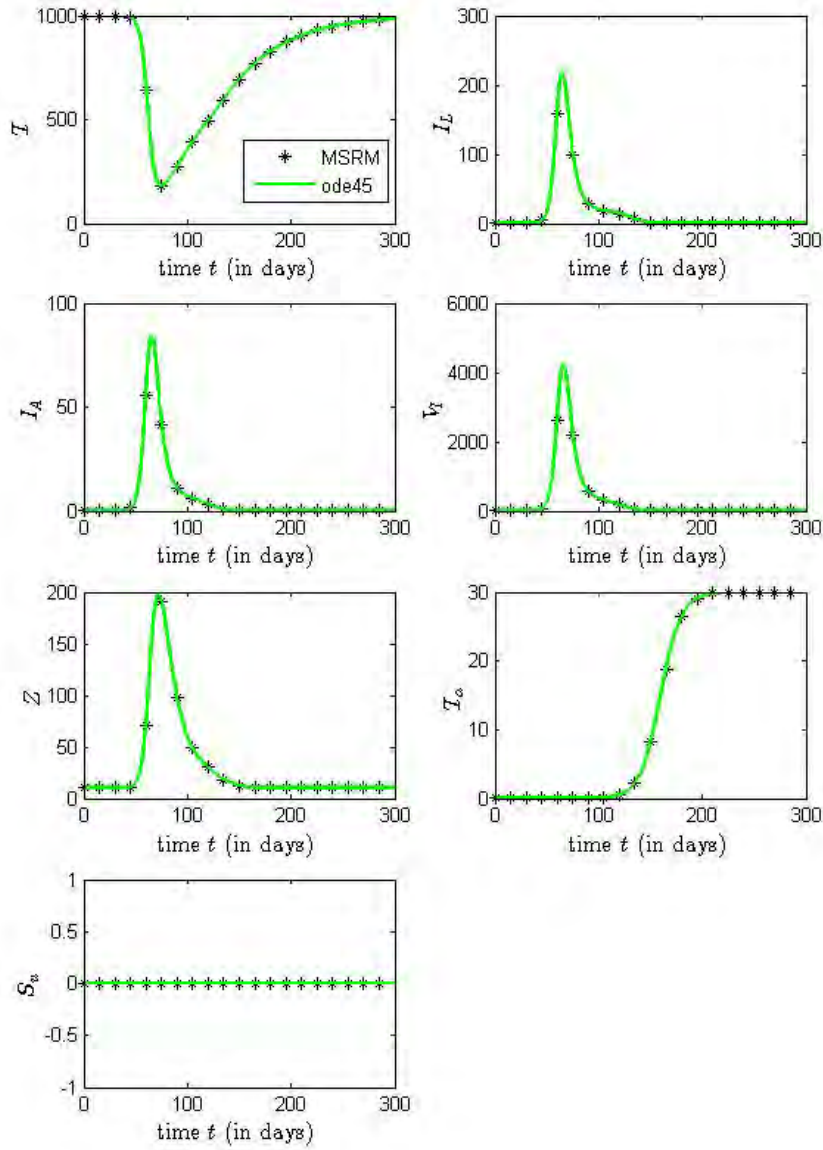


Figure 6.2: Results of the model without Ssu72, when $\pi_1 = 1$.

Case 3: $T_a = 0$ and $S_u = 2.0 \times 10^{-6}$

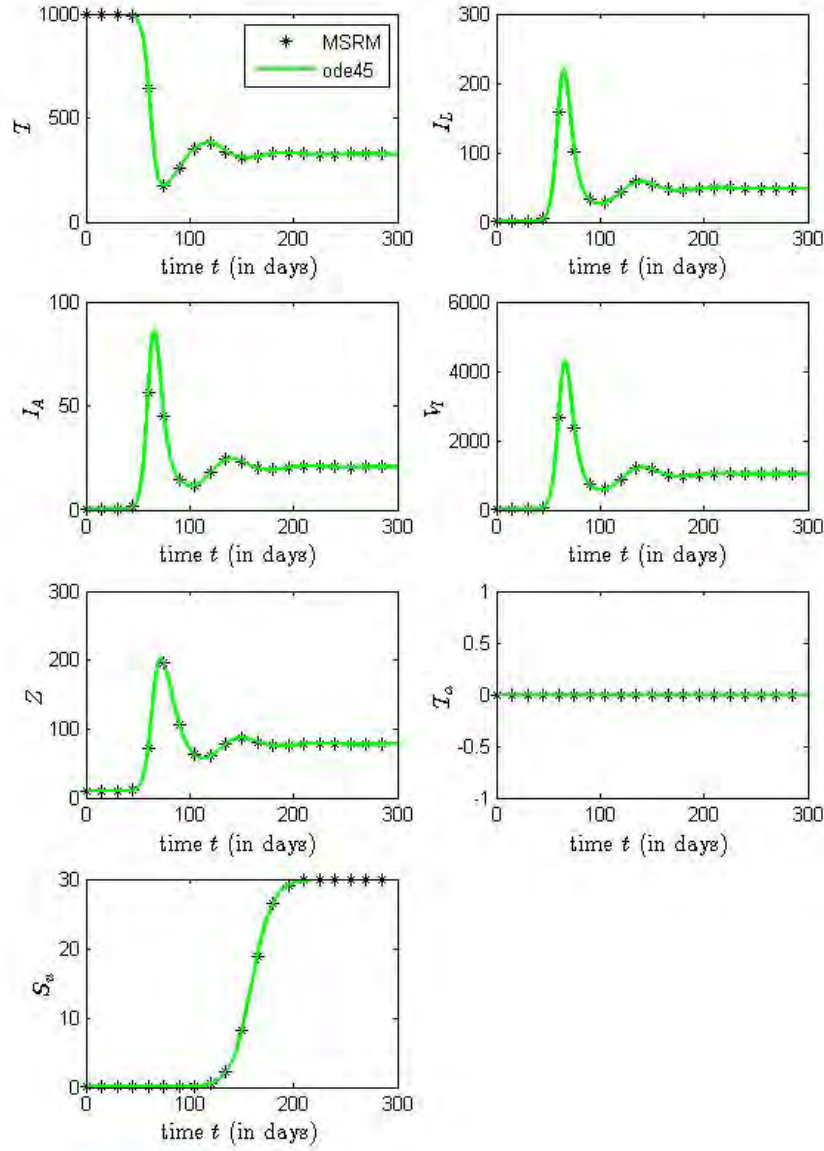


Figure 6.3: Results of the model without Tat, when $\pi_1 = 1$.

Case 4: $T_a = 2.0 \times 10^{-6}$ and $S_u = 2.0 \times 10^{-6}$

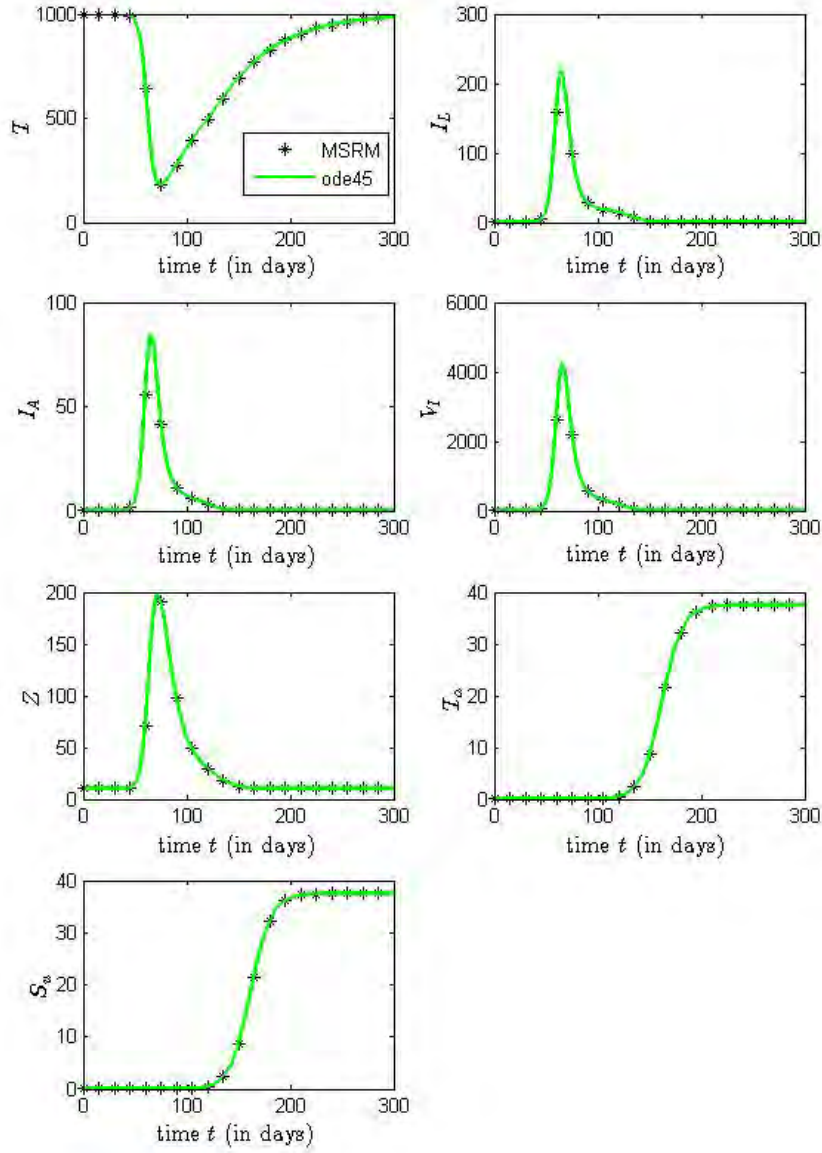


Figure 6.4: Results of the model with Tat and Ssu72, when $\pi_1 = 1$.

Case 1: $T_a = 0$ and $S_u = 0$

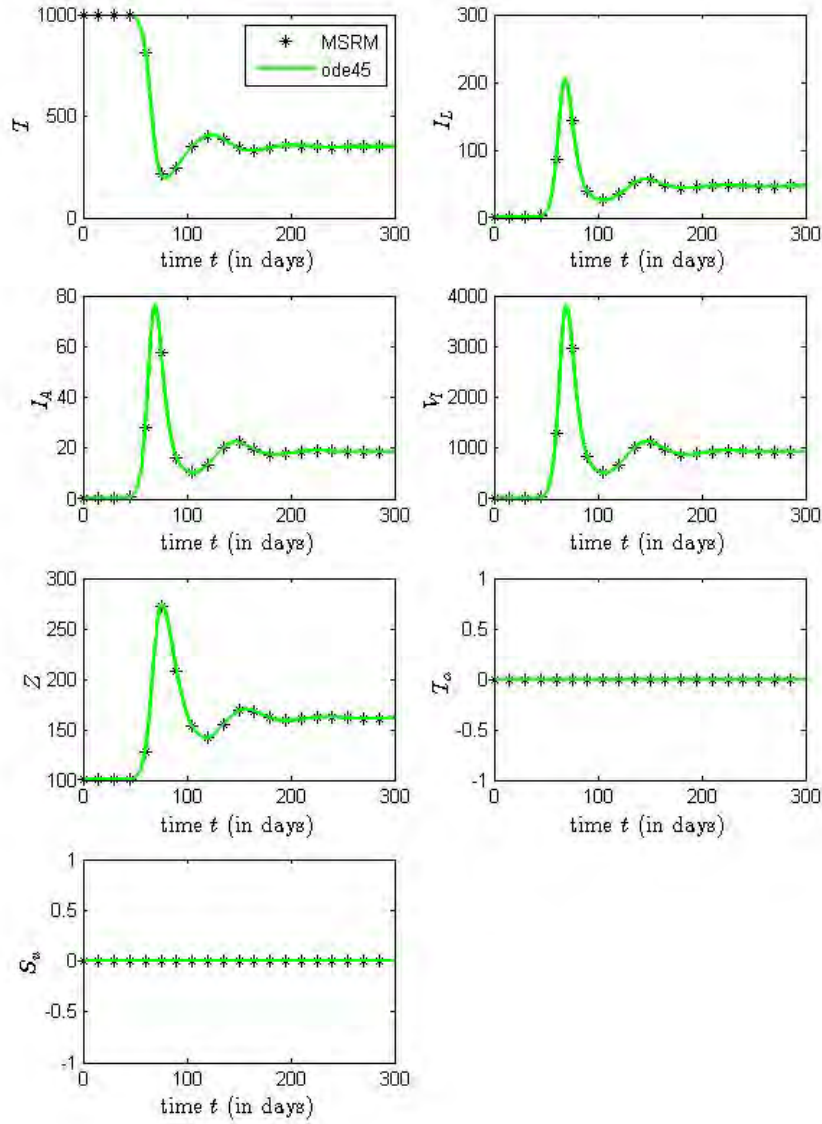


Figure 6.5: Results of the model without Tat and Ssu72, when $\pi_1 = 10$.

Case 2: $T_a = 2.0 \times 10^{-6}$ and $S_u = 0$

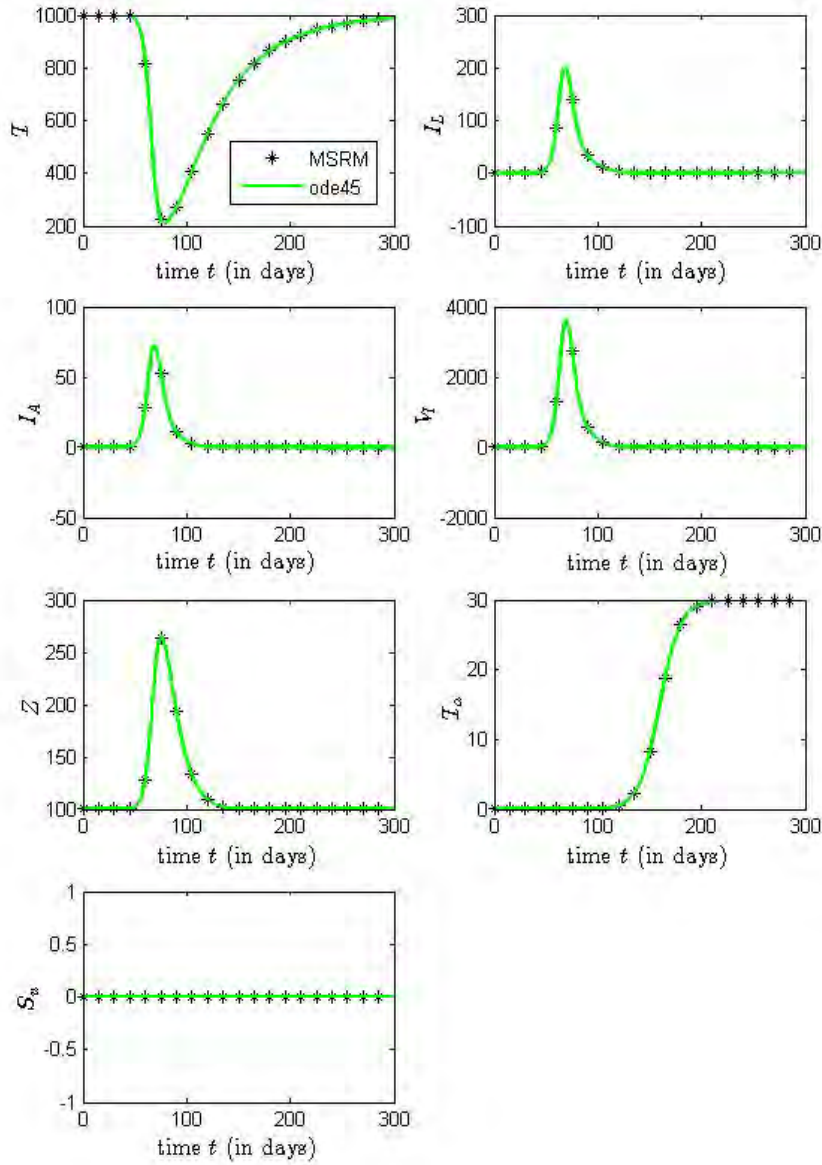


Figure 6.6: Results of the model without Ssu72, when $\pi_1 = 10$.

Case 3: $T_a = 0$ and $S_u = 2.0 \times 10^{-6}$

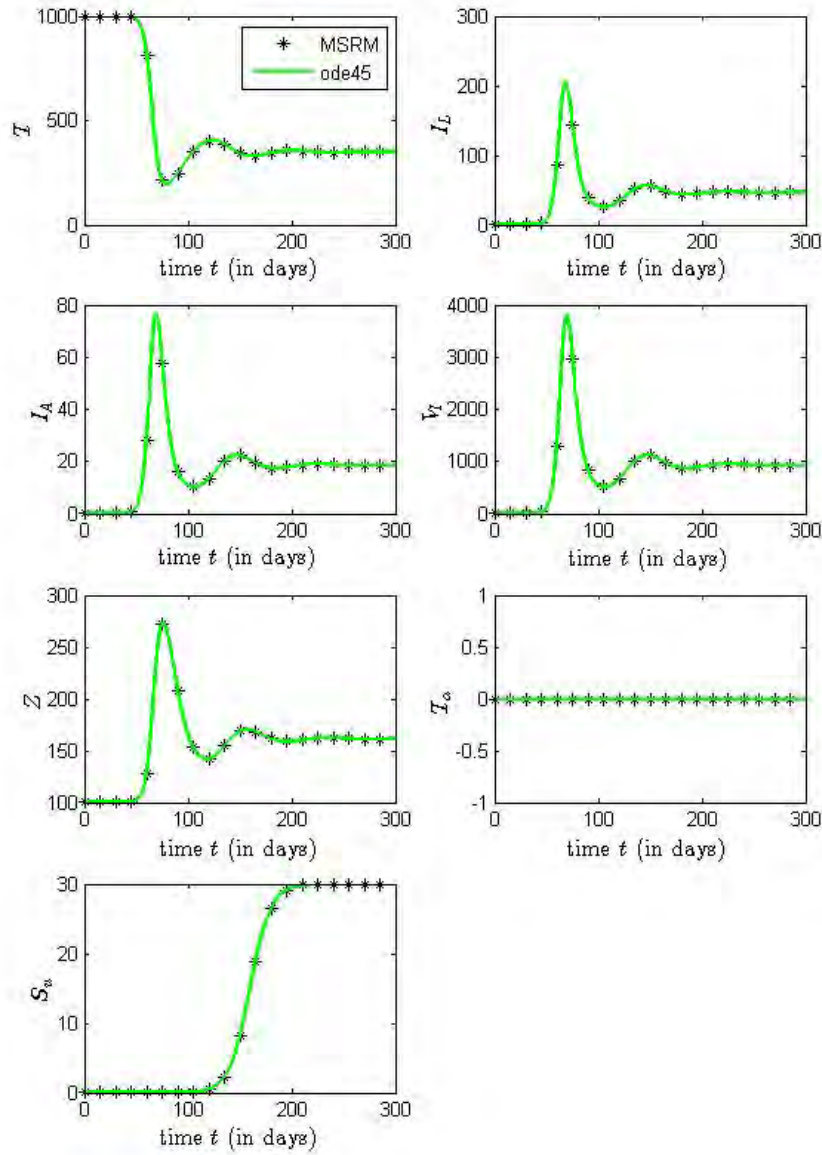


Figure 6.7: Results of the model without Tat, when $\pi_1 = 10$.

Case 4: $T_a = 2.0 \times 10^{-6}$ and $S_u = 2.0 \times 10^{-6}$

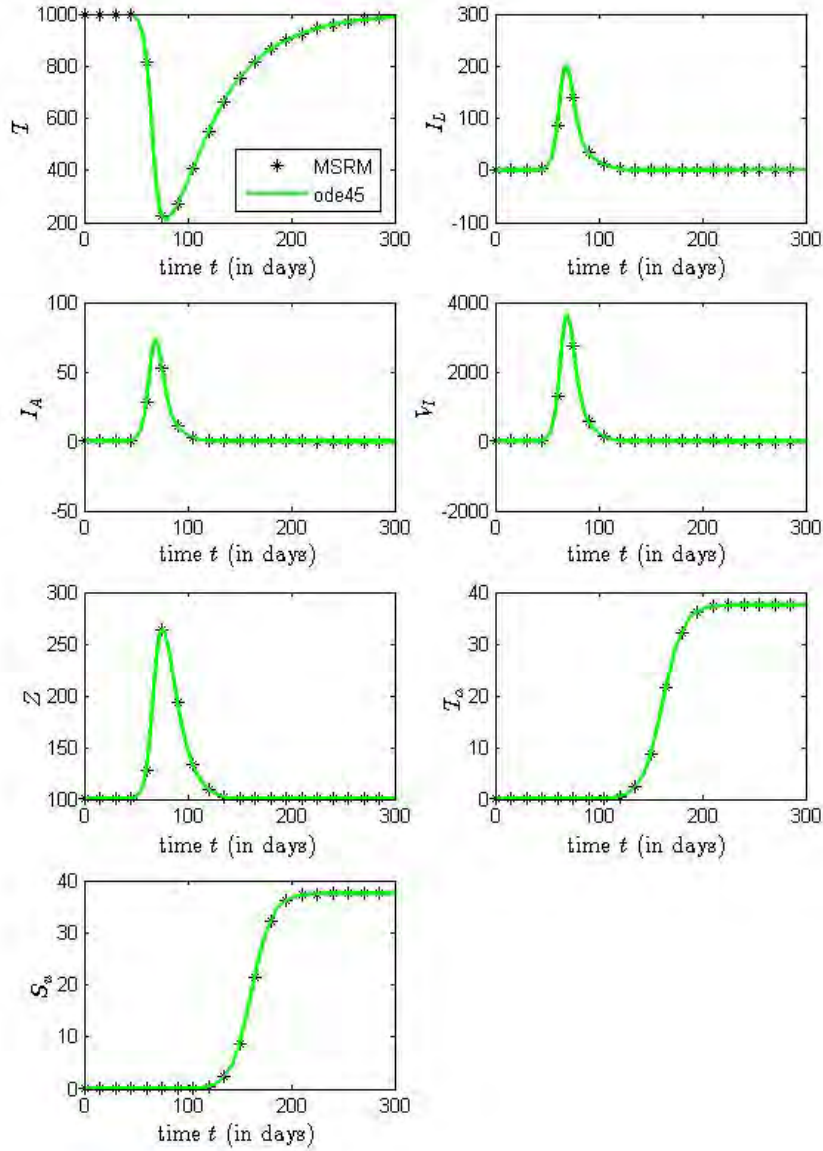


Figure 6.8: Results of the model with Tat and Ssu72, when $\pi_1 = 10$.

We observe in Figure 6.4 and 6.8 that, the two proteins enhance the growth of one another to their maximum values. This in turn causes a more rapid depletion of I_L compared to a case of Tat being present alone consequently, leading to the decrease of viral load decaying to zero. In conclusion, the results suggest that, in the presence of Tat and Ssu72, there is a possibility of wiping out the I_L , virus and recovery of healthy $CD4^+$ T cells. We can therefore, infer that Tat and Ssu72 causes a transition from an endemic equilibrium state to a disease free equilibrium state.

In the presence of Tat, the increase in the effects of $CD8^+$ T cells leads to the significant decrease in viral latent cells and increase in the healthy $CD4^+$ T cells. For case 4, a similar conclusion to case 2 can be reached but there is much more significant decrease in viral load and latently infected $CD4^+$ T cells and best restoration of healthy $CD4^+$ T cells. Hence, the combined effects of Tat and Ssu72 are more significant than the sole effect of each of them.

6.4 Summary

In this chapter we achieved to address the motivation of the study through the analysis of the model presented in chapter 4. Multistage spectral relaxation method was used to analyze the model. Results obtained through MSRM were verified against results obtained through MatLab built-in solver ode45. Figure presenting resulting were presented for cases where we vary the initial conditions for Tat and Ssu72 and also the recruitment rate of $CD8^+$ T cells.

It was shown that the mutualistic combination of Tat and Ssu72 has more significant effect on activation of latently CD4⁺ T cells than the sole effect of each of them. In the following chapter we give a discussion and conclusion of results presented in chapter 6.

Chapter 7

Discussion and conclusion

It is known to date that there is no vaccine to cure HIV-1 infection but rather the antiretroviral drug is used instead. HAART helps to keep the HIV-1 infection in chronic stage and can clear off the infectious virus to undetectable viral load. The challenge with HAART is that it does not target latently infected $CD4^+$ T cells, hence the HIV-1 infection is not eradicated in an infected individual. Thus in this study we have focused on the Tat and Ssu72 known to be responsible for activating the latent virus resting on the $CD4^+$ T cells. The motivation of this study was to study the effects of Tat and Ssu72 on the activation of latently infected $CD4^+$ T cells and the response of immune system.

In chapter 3 we formulated a constant virus production model to capture the dynamics of the HIV-1 infection. The model was shown to be well posed and its solutions to be biologically meaningful. Through analysis of this model we derived threshold to which the infection free and endemic states are glob-

ally stable. For the public health officials these thresholds are critical. They can check which parameters to concentrate onto to develop efficient interventions. On the other hand, one could be interested in the transition of endemic state to disease free state or vice versa, which could be attained through the knowledge of the reproduction number.

The results in chapter 3 suggested that an infected individual will remain infected as long as $R_0 > 1$ and can only be free from a disease when $R_0 \leq 1$. It was also attained that parameters like γ , ω and σ should be considered for transition of endemic state to infection free state. Tat and Ssu72 were known to affect these parameters. In chapter 4 we incorporated Tat and Ssu72 on these parameters to construct activation function, killing rate function and lysis burst function. Imposing these functions on the constant virus production model and combining the resulting model with the system of two equations that captures the role of the Tat and Ssu72, we were able to formulate a model that explains the dynamics of HIV-1 infection better.

In chapter 5, presented an introduction and algorithm of the multistage spectral relaxation method and it was used to analyzed the model presented in chapter 4. This method was recently proposed by Dlamini et al. It was shown to be accurate and reliable. We adopted its in our analysis to demonstrate its accuracy against the well know ode45 MatLab built in it solver. The two methods worked well. Therefore, we can conclude that the results presented in chapter 6 are correct with respect to the structure of the model, parameter and initial values used.

In chapter 6 we investigated the effects of Tat and Ssu72 and the recruitment rate of $CD8^+$ T cells. We noted that in absence of the two protein or of Tat, the latently infected $CD4^+$ T cells were not eradicated irrespective of number of $CD8^+$ T cells present in the immune system. Hence, the infection progresses in an infected individual. However, in the presence of Tat alone or Tat and Ssu72, the results showed that latently infected and the actively infectious $CD4^+$ T cells and the can be eradicated in an infected individual through the response of $CD8^+$ T cells whilst the healthy $CD4^+$ T cells are restored. This result agreed with the assertion in literature, that the eradication of HIV-1 could be achieved by eradicating latent reservoirs. Most importantly, these results shown that the interplay between Tat and Ssu72 can activate the virus resting virus in $CD4^+$ T cells.

7.1 Conclusion

The results suggested that Tat has much influence on the activation of latently infected $CD4^+$ T cells and the killing of infectious infected $CD4^+$ T cells compared to Ssu72. Better effects of Tat can be realised when its functions are enhanced with Ssu72. These results support the findings by a vast number of research, that suggested the activation of resting virus to be a solution to eradication of the HIV infection in an infected individual.

Results do not only show that the viral load could be decreased to zero but they show as well that these proteins can enhance the growth of uninfected

CD4⁺ T cells. We therefore recommend that intervention strategies should be developed that target to enhance the mutual effects of Tat and Ssu72 in activating the latently CD4⁺ T cells. Such interventions should not be used in solitude but in a combination with other effective strategies such as using HAART.

7.2 Further work

From these results, stochastic models can be adopted as the alternative approach to predict the probabilities of infection progression once the virus is introduced into an individual. This aspect makes the models more realistic. Further, using these results as a building blocks to strategies of activation of latent cells, a number of aspects may be incorporated to improve the model, Tat can be manifested as both intracellular or extracellular. In the current study, we only consider intracellular Tat. Incorporating the dynamics of extracellular Tat will also enrich the modeling of activation of latently infected CD4⁺ T cell dynamics.

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